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: Protocol Version 5.0: 08-June-2017

Protocol Version 4.0: 06-June-2017

Protocol Version 3.0: 24-October-2016

Protocol Version 2.0: 05-October-2016

Protocol Version 1.0: 28-September-2016

1. PROTOCOL AND AMENDMENTS

Protocols

- Protocol V5.0 Amendment 4 dated 08Jun2017
    - Amendment 4 Summary of Changes
- Protocol V4.0 Amendment 3 dated 06Jun2017
    - Amendment 3 Summary of Changes
- Protocol V3.0 Amendment 2 dated 24Oct2016
    - Amendment 2 Summary of Changes
- Protocol V2.0 Amendment 1 dated 05Oct2016
    - Amendment 1 Summary of Changes
- Protocol V1.0 dated 28Sep2016

Administrative Letters

- Administrative Letter 1 dated 10Mar2017
- Administrative Letter 2 dated 24May2017
- Administrative Letter 3 dated 02Aug2017

PROTOCOL NUMBER: 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

IND NUMBER: 131,258

Investigational Product	SAGE-217
Clinical Phase	2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted], M.D., Ph.D. [redacted] Phone: [redacted] Email: [redacted]
Sponsor Medical Monitor	[redacted], M.D., M.P.H. Study Physician Phone: [redacted] Email: [redacted]
Date of Original Protocol	28 September 2016
Date of Amendment 1	5 October 2016
Date of Amendment 2	24 October 2016
Date of Amendment 3	06 June 2017
Date of Amendment 4	08 June 2017

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

PROTOCOL SIGNATURE PAGE

Protocol Number:	217-PRK-201
Product:	SAGE-217
IND **No.:**	131,258
Study Phase:	2
Sponsor:	Sage Therapeutics
Date of Amendment 3:	Version 5.0 08 June 2017

Sponsor Approval

[redacted]

08 Jun 2017

[redacted] M.D., Ph.D.
[redacted]
Sage Therapeut[redacted]

Date **(DD /MMMNYYY)**

[redacted]

tJ (;JoL7-

[redacted] Pharm.D, M.S., R.Ph.
[redacted]
Sage Therapeutics

Date (DD/MMM/YYYY)

[redacted]

08 June 2017

[redacted] M.S.H.S.
[redacted]
Sage Therapeutics

Date (DD/MMM/YYYY)

[redacted]

08 June 2017

[redacted] MS
[redacted]
Sage Therapeutics

Date (DD/MMM/YYYY)

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the Clinical Protocol 217-PRK-201 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

CONTACTS IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Research Organization	[redacted]	[redacted]

2. SYNOPSIS

Name of Sponsor/Company:

Sage Therapeutics
215 First Street
Cambridge, MA 02142

Name of Investigational Product:

SAGE-217 Oral Solution

SAGE-217 Capsules

Name of Active Ingredient:

SAGE-217

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

Study centers: Up to 12 centers

Objectives

Primary:

Part A:

- To evaluate the safety and tolerability of SAGE-217 Oral Solution.

Part B:

- To evaluate the effect of SAGE-217 Capsules as an adjunct to antiparkinsonian agent(s) on the severity of PD tremor symptoms.

Secondary:

Part A:

- 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.

Part B:

- 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.

Pharmacokinetic:

- **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.

Endpoints

Primary:

Part A:

- Frequency and severity of adverse events and changes in vital signs, clinical laboratoiy data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Sevedty Rating Scale (C-SSRS). In addition,sleepiness/sedation as assessed by StanfordSleepinessScale (SSS) score.

PartB:

- Improvement in PD tremor as assessed by changes in the MDS UPDRS Pait WIII tremor score (defined as the sum of MDS-UPDRSitems 2.10, 3.15, 3.16, 3.17 and 3.18).

Secondar y:

Part A:

- Improvement in PD motor symptoms as assessed by changes in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS)- Pait III (MotorExainination) score.

PartB:

- Improvement in PD motor symptoms as assessed by changes in the MDS-UPDRS- Pait III total score.
- Improvement in PD nonmotor and motor aspects of expeiiences of daily living as assessed by the MDS-UPDRS - Pait I and Pait II scores, respectively.
- Improvement in PD overall symptoms as assessed by changes in the MDS-UPDRS- Paits I-IV total score.
- Frequency and severity of adverse events and changes in vital signs, clinical laboratoiy data, electrocai·diogram (ECG) pai·ametes, and suicidal ideation using the Columbia-SuicideSevedty Rating Scale (C-SSRS).

Pharmacokinetic:

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

Exploratory:

[redacted]

[redacted]

Methodology:

This study will assess the safety, tolerability, pharmacokinetics (PK) and effectiveness of SAGE-217. For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol.

There are two parts , Part A and Part B, described below.

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

All subjects will continue to take their antiparkinsonian agent(s) including immediate-release oral Levodopa on the day of admission (Day -1) and in the AM only 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. Subjects not tolerating 30 mg will receive 20 mg, and subjects not tolerating 20 mg will receive 10 mg on subsequent days. 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 in order to inform the conduct of Part B.

Assessments will be performed periodically during the study as outlined in the Schedule of Events for Part A (Table 2).

Part B: Open-label with evening (PM) dosing, 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 adverse event 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 adverse event 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. 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 B (Table 3).

Number of subjects (planned):

Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A 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).

Inclusion Criteria:

1. Subject has signed an informed consent form (ICF) before any study-specific procedures are performed.
2. Subject is between 40 and 75 years of age, inclusive.
3. Subject has a diagnosis of idiopathic PD based on modified UK Brain Bank Criteria (modified to allow individuals with a family history of PD) (Hughes 1992; Appendix 1).
4. **Part A**: Subjects with PD with a duration of less than 7 years and must meet the criteria for Hoehn and Yahr stage 2 or stage 3 (Appendix 2).
   Part B: Subjects with PD and must meet the criteria for Hoehn and Yahr stage 1-4 (Appendix 2) assessed during the "on" period (assumed to be within 2 hours of dosing with antiparkinsonian agent(s)), and have a tremor with a MDS-UPDRS Part II/III tremor score of ≥8 (sum of items: 2.10, 3.15, 3.16, 3.17 and 3.18) AND a MDS-UPDRS item score ≥3 in at least one limb (from items 3.15, 3.16, or 3.17). Inclusion criteria tremor scores must be assessed during "on" periods during the screening and Day -1 visit.
5. **Part A**: Subject has a stable dose of antiparkinsonian agent(s) including immediate-release oral Levodopa or Carbidopa-Levodopa (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.
   Part B: Subject is receiving a stable dose of antiparkinsonian agent(s) (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.
6. **Part A only**: Subject is willing to discontinue his/her treatment with immediate-release oral Levodopa or Carbidopa-Levodopa for at least 8 hours prior to dosing with SAGE-217.
7. **Part A**: Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) or amantadine at least 5 days prior to the day of admission (Day -1).
   Part B: Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) by Day -6 or amantadine by Day -10.
8. Subjects taking an antidepressant drug, sleep medication, or neuroleptic must have been on a stable dose for at least 1 month prior to the baseline visit.
9. Subjects must have a MoCA score of >22.
10. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests.
11. **Part A**: Female subjects must agree to practice a highly effective method of birth control while on study through completion of the last follow-up visit. If a subject discontinues early after receiving

a dose of SAGE-217, then the subject must continue this method of birth control for at least 7 days following the last dose of study drug. Highly effective methods of birth control include combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence.
Part B: Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause) and/or surgically sterile:

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation.
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner.
- Sexual abstinence (no sexual intercourse).

12. Male subjects must agree to practice a highly effective method of birth control while on study, and for 13 weeks after receiving the last dose of study drug. Effective methods of birth control include sexual abstinence, vasectomy, or a condom with spermicide (men) in combination with their partner's highly effective method.
13. Males must be willing to abstain from sperm donation and females from donating eggs while on study through 13 weeks after receiving the last dose of study drug.
14. **Part B only**: Subjects who participated in Part A and meet all eligibility criteria for Part B must have tolerated at least 20 mg SAGE-217 in Part A, otherwise they are ineligible.

Exclusion Criteria:

1. Subjects with a known hypersensitivity to SAGE-217 Oral Solution or its major excipient, HPβCD (**Part A**) or SAGE-217 Capsule or its excipients (**Part B**).
2. **Part A**: Subjects with early PD (Hoehn and Yahr stage 1) or advanced PD (Hoehn and Yahr stage 4 or stage 5).
   Part B: Subjects with advanced PD (Hoehn and Yahr stage 5).
3. Subjects with any medical or psychiatric condition that jeopardizes/compromises his/her ability for participation. This includes schizophrenia spectrum and other psychotic disorders, substance-related and addictive disorders, feeding and eating disorders, bipolar and related disorders, structural brain disease including but not limited to history of encephalitis or hydrocephalus and history of clinically significant stroke, or anticipating starting psychotherapy or behavior therapy during the course of the study or who started psychotherapy or behavior therapy within 30 days prior to Day 1.
4. Subjects with a history of:
   a. Electroconvulsive therapy;

b. Stereotaxic brain surgery (deep brain stimulation) for PD;
c. History of suicide attempt within 2 years, or has answered YES to questions 3, 4, or 5 on the C SSRS at the screening or Day -1 visits, or has current suicidal ideation; or
d. Impulse control disorder.

5. **Part A**: Subjects with severe depression as defined by a BDI-II score >19.
6. **Part B**: Subject has recent exposure (14 days prior to the Day -1 visit) to tremorogenic drugs, as defined in Appendix 4.
7. Subjects with Type I or Type II diabetes mellitus.
8. Subjects with presence of drug-induced parkinsonism (eg, metoclopramide, flunarizine), metabolic identified neurogenetic disorders (eg, Wilson's disease), encephalitis, or other atypical Parkinsonian syndromes (eg, progressive supranuclear palsy, multiple system atrophy).
9. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.
10. Subject has clinically significant abnormal physical examination OR 12-lead ECG at the screening or admission visits. NOTE: QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study. ECG may be repeated once if initial values obtained are outside the specified limits.
11. Subject has a history, presence and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies 1 and 2.
12. Subject has exposure to another investigational medication or device within 30 days prior to Day 1.
13. Subject has donated one or more units of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing (1 unit = 450 mL).
14. Subject is unwilling or unable to comply with study procedures.
15. Subjects has used any known strong inhibitors and/or inducers of cytochrome P450 (CYP)3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.

Investigational product, dosage and mode of administration:

Part A: SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dose.

Part B: SAGE-217 Capsules are available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients. For Part B, capsules will be available in 5-mg, 10-mg and 20-mg dose strengths. Subjects will be administered two capsules per dose.

Duration of treatment:

Part A and Part B:
Screening Duration: up to 28 days per part
Treatment Period: 7 days per part
Follow-up: 7 days per part

Planned Study Duration per Subject: approximately 42 days if participating in one part only (up to 84 days if participating in both Parts A and B)

Reference therapy, dosage, and mode of administration:

Not applicable; Part A and Part B are open-label with all subjects receiving SAGE-217.

Criteria for evaluation:

Safety and tolerability:

Safety and tolerability of study drug will be evaluated by vital signs, clinical laboratory measures, ECGs, physical examinations, concomitant medication usage, C-SSRS, and adverse event reporting. Sleepiness/sedation will be assessed by the SSS in Part A only.

Efficacy:

Part A:

- Improvement in PD motor symptoms and overall symptoms will be assessed by changes in the MDS UPDRS Part III score and MDS-UPDRS Parts I-IV total score at various time points.

Part B:

- Improvement in PD tremor as assessed by changes in the 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).
- 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.

Pharmacokinetics:

Plasma will be collected to assay for concentrations of SAGE-217 and possibly SAGE-217 metabolites in Part A and Part B.

Part A: The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), the distributional half-life and terminal half-life ($t_{1/2}$), and steady-state drug concentration in the plasma (C_{ss}).

Part B: Area under the curve (AUC), C_{max}, and trough concentration (C_{0h}) at steady-state will be estimated for each individual using the most recent applicable Population PK model.

Statistical Methods:

Sample Size Calculation

Approximately 18 subjects will be enrolled in Part A. 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). The sample size for Part A and Part B was selected based on clinical and not statistical considerations.

Study Populations

The safety population, defined as all subjects who are administered at least one dose of study drug, will be used to provide descriptive summaries of safety.

The efficacy population, defined as all subjects in the safety population who receive at least one dose of study drug and have at least one postdose MDS-UPDRS evaluation, will be used to analyze efficacy data.

The PK population will consist of all subjects in the safety population with at least one plasma sample with sufficient plasma concentrations for PK evaluations and will be used to summarize PK data.

Separate populations will be defined for each part of the study.

General Considerations

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

Safety Analysis

Adverse events will be coded using Medical Dictionary for Regulatory Activities™ (MedDRA). The overall incidence of adverse events will be displayed by System Organ Class (SOC), preferred term, dose group, and cohort. Incidence of adverse events will also be presented by maximum severity and relationship to study drug. Vital signs, clinical laboratory measures, ECG, and C-SSRS data will be summarized by dose group and total, where applicable. Out-of-range safety endpoints may be categorized as low or high, where applicable. Subject listings will be provided for all safety data.

Efficacy Analysis

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data.

An interim analysis of 10 subjects completing Part A is planned to inform Part B study conduct. No formal interim analysis for Part B subjects is planned.

Pharmacokinetic Analysis

Drug concentrations and pharmacokinetic parameters will be summarized using appropriate descriptive statistics and listed by subject.

Table 2: Schedule of Events: Part A (Open-Label)

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]											

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)
[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]; [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 Admission (Day -1); predose for Day 4, Day 6, and Day 8; and Day 14

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

[d] Vital Signs: Screening and 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. 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 be used 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 MOAAIS: Predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Confinement Days 3, 4, 5, 6, and 7; in AM of Day 8; and Day 14. The MOAAIS 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.

[redacted]

p Plasma PK sampling times (±5 minutes): Day 4 predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours post dose; predose 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

Table 3: Schedule of Events: Part B (Open-Label)

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[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	X									
CBC/Serum Chemistry[b]	X	X[c]				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	X		
MDS-UPDRS (Part III only)[k]			X	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)
Plasma PK Samples[r]			X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X
Administer SAGE-217[s]			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 da ys); at 8AM (±1 hour) on Day l; 12 (±15 1ninutes) 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 antiparkinsonianagent(s).

k MDS-UPDRS (Part II/III only): 12 and 23 **(±15**1ninutes) hours postdose on Confinement Days 1, 2, 3, 4, *5,* and 6. MDS-UPDRS Part 11/111s hould take place during the "on" period AND within 2 hours of dosing with antiparkinsonian agent(s).

I [redacted]

r Plasma PK sampling times (±1 hour): predose and 13 hours postdose on Day l; and 13 hours postdose on Days 2 through 7.

[5] SAGE-217 Capsules are to be adrninistered in the evening (8PM ±30 minutes) with food.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

1. TITLE PAGE 1
2. SYNOPSIS 5
3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 19
4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 24
5. INTRODUCTION 26
5.1. Background of Parkinson's Disease and Unmet Medical Need 26
5.2. SAGE-217 27
5.3. Summary of Nonclinical and Clinical Experience with SAGE-217 27
5.3.1. Nonclinical Studies with SAGE-217 27
5.3.2. Clinical Experience 27
5.4. Potential Risks and Benefits 29
6. TRIAL OBJECTIVES AND PURPOSE 31
6.1. Primary Objective 31
6.2. Secondary Objectives 31
6.3. Pharmacokinetic Objectives 31
6.4. Endpoints 31
6.4.1. Primary Endpoints 31
6.4.2. Secondary Endpoints 32
6.4.3. Pharmacokinetic Endpoints 32
6.4.4. Exploratory Endpoints 32
7. INVESTIGATIONAL PLAN 34
7.1. Overall Study Design 34
7.2. Number of Subjects 35
7.3. Treatment Assignment 35
7.4. Dose Adjustment Criteria 35
7.5. Criteria for Study Termination 36
8. SELECTION AND WITHDRAWAL OF SUBJECTS 38
8.1. Subject Inclusion Criteria 38
8.2. Subject Exclusion Criteria 39

8.3. Subject Withdrawal Criteria 41
9. TREATMENT OF SUBJECTS 42
9.1. Description of Study Drug Treatment 42
9.1.1. Part A 42
9.1.2. Part B 42
9.2. Concomitant Medications 42
9.2.1. Prior/Concomitant Medications 42
9.2.2. Prohibited Medications 43
9.3. Treatment Compliance 43
9.4. Randomization and Blinding 43
10. STUDY DRUG MATERIALS AND MANAGEMENT 44
10.1. Study Drug 44
10.1.1. SAGE-217 Oral Solution 44
10.1.2. SAGE-217 Capsule 44
10.2. Study Drug Packaging and Labeling 44
10.3. Study Drug Storage 44
10.4. Study Drug Preparation 45
10.5. Administration 46
10.6. Study Drug Accountability 46
10.7. Study Drug Handling and Disposal 46
11. ASSESSMENT OF EFFICACY 47
11.1. Movement Disorder Society – Unified Parkinson's Disease Rating Scale 47
11.2. Exploratory Endpoints 48
[redacted] [redacted] 48
[redacted] [redacted] 49
[redacted] [redacted] 49
[redacted] [redacted] 49
[redacted] [redacted] 50
[redacted] 50
12. PHARMACOKINETICS 52
12.1. Blood Sample Collection 52
12.2. Storage and Shipment of Pharmacokinetic Samples 52

12.3. Sample Analysis 52
13. ASSESSMENT OF SAFETY 53
13.1. Safety and Tolerability Parameters 53
13.1.1. Demographic/Medical History 53
13.1.2. Vital Signs 53
13.1.3. Weight and Height 53
13.1.4. Physical Examination 53
13.1.5. Electrocardiogram (ECG) 53
13.1.6. Laboratory Assessments 54
13.1.6.1. Hematology 54
13.1.6.2. Blood Chemistry 54
13.1.6.3. Urinalysis 54
13.1.6.4. Virus Serology 55
13.1.6.5. Pregnancy Screen 55
13.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS) 55
13.1.8. Stanford Sleepiness Scale (SSS) 55
13.1.9. Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) 55
13.2. Adverse and Serious Adverse Events 56
13.2.1. Definition of Adverse Events 56
13.2.1.1. Adverse Event 56
13.2.1.2. Suspected Adverse Reaction 56
13.2.1.3. Serious Adverse Event 56
13.2.1.4. Recording Sedation as an Adverse Event 57
13.2.2. Pregnancy 57
13.3. Relationship to Study Drug 57
13.4. Recording Adverse Events 58
13.5. Reporting Serious Adverse Events 58
14. STATISTICAL METHODS AND CONSIDERATIONS 60
14.1. Data Analysis Sets 60
14.2. Handling of Missing Data 60
14.3. General Considerations 60
14.4. Demographics and Baseline Characteristics 60

14.5. Efficacy Endpoints....60
14.5.1. Secondary Efficacy Endpoints....61
14.5.2. Exploratory Efficacy Endpoints....61
14.6. Safety and Tolerability Analyses....61
14.6.1. Adverse Events....61
14.6.2. Vital Signs....61
14.6.3. Physical Examinations....62
14.6.4. 12-Lead ECG....62
14.6.5. Clinical Laboratory Evaluations....62
14.6.6. Columbia-Suicide Severity Rating Scale (C-SSRS)....62
14.6.7. Stanford Sleepiness Scale (SSS)....62
14.6.8. Modified Observer's Assessment of Alertness/Sedation (MOAA/S)....62
14.6.9. Prior and Concomitant Medications....62
14.7. Pharmacokinetic Analysis....63
14.8. Determination of Sample Size....63
14.9. Changes From Protocol Specified Analyses....63
15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS....64
15.1. Study Monitoring....64
15.2. Audits and Inspections....64
15.3. Institutional Review Board (IRB)....65
16. QUALITY CONTROL AND QUALITY ASSURANCE....66
17. ETHICS....67
17.1. Ethics Review....67
17.2. Ethical Conduct of the Study....67
17.3. Written Informed Consent....67
18. DATA HANDLING AND RECORDKEEPING....68
18.1. Inspection of Records....68
18.2. Retention of Records....68
18.3. Confidentiality....68
19. PUBLICATION POLICY....70
20. LIST OF REFERENCES....71
21. APPENDICES....73

APPENDIX 1. UNITED KINGDOM BRAIN BANK CRITERIA 74
APPENDIX 2. HOEHN AND YAHR STAGING CRITERIA 75
APPENDIX 3. ANTICHOLINERGIC DRUGS 76
APPENDIX 4. TREMOROGENIC DRUGS 77
APPENDIX 5. MOVEMENT DISORDER SOCIETY-UNIFIED PARKINSON'S DISEASE RATING SCALE (MDS-UPDRS) 79
[redacted] 80
[redacted] 83
[redacted] 86
[redacted] 87
APPENDIX 10. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION AND SINCE LAST VISIT VERSION 90
APPENDIX 11. STANFORD SLEEPINESS SCALE (SSS) 96
APPENDIX 12. MODIFIED OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (MOAA/S) 97

LIST OF TABLES

Table 1: Emergency Contact Information 4
Table 2: Schedule of Events: Part A (Open-Label) 13
Table 3: Schedule of Events: Part B (Open-Label) 16
Table 4: Abbreviations and Specialist Terms 24
Table 5: Batch Formula for 125 mL of Stock SAGE-217 Oral Solution 6 mg/mL 45
Table 6: Rating Scale for the MDS-UPDRS 47

LIST OF FIGURES

Figure 1: Study Design of Part A 37
Figure 2: Study Design of Part B 37

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ALT	alanine aminotransferase
AM	morning
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
[redacted]	[redacted]
BMI	body mass index
CBC	complete blood count
C_{max}	maximum plasma concentration
CRF	case report form
CS	clinically significant
Css	steady-state drug concentration in the plasma
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic CRF
EP	European Pharmacopeia
GABA	γ aminobutyric acid
$GABA_A$	γ aminobutyric acid-ligand gated chloride channel
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPβCD	hydroxypropyl-β-cyclodextrin
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
Levodopa/Carbidopa	Levodopa or Carbidopa-Levodopa
MDS	Movement Disorder Society
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
MoCA	Montreal Cognitive Assessment
MTD	maximum tolerated dose
n	number
NCS	not clinically significant
NF	National Formulary
PD	Parkinson's disease
[redacted]	[redacted]
PK	pharmacokinetic(s)
PM	evening
QTcF	QT interval calculated using the Fridericia method
SOC	system organ class
SRC	Safety Review Committee
SSS	Stanford Sleepiness Scale
TEAE	treatment-emergent adverse event
$t_{1/2}$	terminal half-life
t_{max}	time to reach maximum concentration
USP	United States Pharmacopeia
WHO	World Health Organization

5. INTRODUCTION

5.1. Background of Parkinson's Disease and Unmet Medical Need

Parkinson's disease (PD) is a chronic progressive neurodegenerative condition that affects the motor, autonomic, cognitive, and sensory systems. Parkinson's disease is the second most common neurodegenerative disorder (Bergman 2002) and is associated with a massive loss of dopaminergic cells in the substantia nigra, leading to dopamine hypofunction and alteration of the basal ganglia circuitry. Dopamine neurons are under the control of the excitatory glutamatergic and inhibitory γ-aminobutyric acid (GABA) systems. Imbalance between the glutamatergic and GABA systems may contribute to excitotoxicity and dopaminergic cell death.

The motor symptoms of PD have been linked with a loss of dopamine neurons in the substantia nigra pars compacta and a consequential reduction in the level of dopamine input in the striatum (Siderowf 2012). These symptoms evolve slowly and are characterized by the progression of tremor, rigidity, bradykinesia, and postural instability. Tremor caused by PD can appear as either a resting tremor or an action tremor. The most typical tremor of PD is a "pill-rolling" rest tremor between the thumb and index finger. Not everyone with PD develops a tremor, and those who do experience tremor may have symptoms that come and go. Typically, PD tremor starts in the fingers of one hand before spreading to affect the rest of the arm. Tremor can also spread to affect the foot on the same side of the body and, after several years, the tremor can spread to affect the other side of the body. Without treatment, PD tremor usually worsens over time.

At present, there is no cure for PD. The core symptoms are caused by the degeneration of dopamine-producing neurons and, therefore, treatment consists of dopamine replacement. While enormous progress has been made in the treatment of PD over the past half century, levodopa remains the most potent drug for controlling PD symptoms (Jankovic 2008). The addition of carbidopa, a peripheral dopa decarboxylase inhibitor, enhances the therapeutic benefits of levodopa. However, levodopa therapy is frequently associated with motor complications, and the appropriate time to initiate levodopa therapy continues to be debated (Stern 2004; Weiner 2004). The majority of patients treated with levodopa experience motor fluctuation, dyskinesia or other complications after 5 years of treatment (Jankovic 2005).

Neurosteroids, a group of steroid hormones synthesized in the brain, modulate the function of several neurotransmitter systems. The substantia nigra expresses high concentrations of allopregnanolone, a neurosteroid that positively modulates the action of GABA at γ-aminobutyric acid-ligand gated chloride channel ($GABA_A$) receptors. In PD patients, decreased plasma and cerebrospinal fluid levels of the neurosteroid allopregnanolone and 5α-dihydroprogesterone have been observed (di Michele 2003).

Parkinson's disease is the second most common chronic neurodegenerative disease, affecting about 1 million people in the United States and more than 4 million people worldwide. It has a devastating effect on patients and is often accompanied by tremendous physical and emotional burden not only for the patients but also for their families and friends. As the size of the elderly population grows, the burden of PD is projected to grow substantially over the next few decades. To date, the therapy of PD is symptomatic, aimed at ameliorating motor symptoms. Although the goal of therapy is to reverse the functional disability, abolition of all symptoms and signs is not currently possible, even with high doses of medication. Thus, there is a growing need for

innovative new treatments to prevent, delay onset, or alleviate symptoms of PD. Neurosteroids act as neuroprotectants and as $GABA_A$-receptor agonists in the physiology and pathology of the basal ganglia, impact dopaminergic cell activity and survival, and may therefore represent potential therapeutics in PD.

5.2. SAGE-217

SAGE-217 is a positive allosteric modulator of the $GABA_A$ receptor and thus is expected to be of benefit for the treatment of PD.

Two dosage forms of SAGE-217 for oral administration will be used in this study (SAGE-217 Oral Solution in Part A and SAGE-217 Capsules in Part B).

SAGE-217 Oral Solution 6 mg/mL (40% w/w aqueous hydroxypropyl-β-cyclodextrin [HPβCD] with 0.025 mg/mL sucralose) is a non-viscous, clear solution.

SAGE-217 Capsules are available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the active, SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients.

5.3. Summary of Nonclinical and Clinical Experience with SAGE-217

5.3.1. Nonclinical Studies with SAGE-217

In nonclinical studies of SAGE-217, sedative-hypnotic effects were consistently observed at higher doses in both in vivo pharmacology studies and in toxicology studies. The sedative-hypnotic impairments seen with SAGE-217 were typical for $GABA_A$-positive modulators, ranging from hyperexcitability and ataxia at the lower doses through deep sedation and ultimately anesthesia at higher doses. Depth and duration of sedation demonstrated a clear dose response over the range tested, with evidence of tolerance occurring with continued exposure. Tolerance to the effects of SAGE-217 on motor incoordination was not observed after 7 days of dosing.

The compound has been assessed in 14-day rat and dog toxicology studies with daily administration of SAGE-217 as a solution in HPβCD in dogs and Labrasol® in rats. The no observed adverse effect level was 3 mg/kg (females) and 22.5 mg/kg (males) in rats and 2.5 mg/kg in dogs. There were no adverse effects in dogs or rats in the main toxicology studies. A single observation of mortality occurred in one female rat at the high dose in a toxicokinetic study that was suspected to have been related to exaggerated pharmacology. Additional toxicology and pharmacology information is provided in the Investigator's Brochure.

5.3.2. Clinical Experience

To date, two clinical studies employing SAGE-217 Oral Solution are clinically complete and final clinical study reports are pending. Discussions of pharmacokinetic (PK) data are limited to the single-ascending dose, food effect, and essential tremor cohorts from Study 217-CLP-101 and the multiple-ascending dose and drug-drug interaction cohorts from Study 217-CLP-102. Discussions of safety data are limited to the single-ascending dose cohorts in Study 217-CLP-101 and the multiple-ascending dose cohorts in Study 217-CLP-102. In addition, one

clinical study of the safety, tolerability, PK, and relative bioavailability SAGE-217 Capsules is clinically complete and the final study report is pending. The results of this study (217-CLP-103) are briefly described below.

Study 217-CLP-101 was a first-in-human, four-part study that assessed the effects of a single dose of SAGE-217 Oral Solution. The study was a double-blind, placebo-controlled, single-ascending dose design in healthy adult volunteers, with the objective of identifying the maximum tolerated dose (MTD) and PK profiles of SAGE-217 Oral Solution. Subjects in each of the single-ascending dose cohorts received a single dose of study drug, either SAGE-217 Oral Solution (six subjects) or placebo (two subjects), with SAGE-217 Oral Solution doses of 0.25 mg, 0.75 mg, 2 mg, 5.5 mg, 11 mg, 22 mg, 44 mg, 55 mg, and 66 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the Safety Review Committee (SRC) and agreement reached that it was safe to increase the dose. The MTD was determined to be 55 mg. Two cohorts, 6 subjects each, received SAGE-217 Oral Solution in an open-label manner (one cohort received 50% of the MTD [22 mg] to study the food effects and the other cohort received the MTD [55 mg] to study the effects on subjects with essential tremor). SAGE-217 Oral Solution was orally bioavailable, demonstrated dose-linear PK from the lowest (0.25 mg) through the highest (66 mg) dose, and supported once-daily oral dosing with food. In addition, the pharmacodynamic effects of the SAGE-217 Oral Solution MTD were assessed in placebo-controlled, blinded, crossover electroencephalogram cohorts of 8 subjects each; one cohort received 50% of the MTD (22 mg) and the other received the MTD (55 mg).

Study 217-CLP-102 was a two-part study that assessed the effects of multiple-ascending doses of SAGE-217 Oral Solution. The study was a double-blind, placebo-controlled, multiple-ascending dose study in healthy adult volunteers. Subjects in each of the multiple-ascending dose cohorts received study drug, either SAGE-217 Oral Solution (nine subjects) or placebo (three subjects), once daily for 7 days, with SAGE-217 Oral Solution doses of 15 mg, 30 mg, and 35 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the SRC and agreement reached that it was safe to increase the dose. The MTD was determined to be 30 mg. It was observed that subjects receiving the drug in the evening did better in terms of tolerability compared to when they received the drug in the morning. A fourth cohort of 12 subjects received 30 mg of SAGE-217 Oral Solution in an open-label manner to study drug-drug interactions. SAGE-217 Oral Solution is not likely to induce the metabolism of cytochrome P450 (CYP)2B6 or CYP3A4 substrates. SAGE-217 Oral Solution was orally bioavailable and suitable for once-daily oral dosing at night time with food.

SAGE-217 Oral Solution was generally well tolerated. In both Phase 1 studies (217-CLP-101 and 217-CLP-102), doses were escalated until the stopping criteria were met. Most adverse events were reported as mild or moderate in intensity, and there were no serious adverse events reported in either study. In addition, none of the observed adverse events resulted in discontinuation of the study drug. At doses planned for further study, the observed sedation was mild, transient, and associated with daily peak exposure. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, dizziness, euphoric mood, fatigue, tremor, and muscle twitching, reported most frequently in the highest dose group (66 mg). Some changes in mean blood pressure and heart rate were observed after single doses of 44 mg and greater. After multiple doses of 30 mg (morning [AM] or evening [PM]) or 35 mg (AM) over 7 days, there was no evidence of changes in mean vital sign measures even though Day 7 plasma

concentrations approximated that of the highest single dose in the single-ascending dose study. Subjects seemed to tolerate SAGE-217 Oral Solution better when given as night time dosing.

The safety, tolerability, PK, and relative bioavailability of the SAGE-217 Capsules were assessed in a Phase 1 randomized, open-label, cross-over study (Study 217-CLP-103). In the fasted state, SAGE-217 Capsules demonstrated reduced exposure in terms of maximum (peak) plasma concentration (C_{max}) and area under the curve from zero to the time of the last quantifiable concentration (AUC_{last}) compared to SAGE-217 Oral Solution. SAGE-217 Capsules administered in the fed state (with standard and high-fat meal) showed increased exposure compared to the fasted state and approximately equivalent exposure in terms of geometric mean AUC_{last} compared to SAGE-217 Oral Solution; however, the C_{max} for SAGE-217 Capsules was reduced by approximately 50% when compared with SAGE-217 Oral Solution. Based on these study results, exposures with SAGE-217 Capsules are anticipated to be equal to or less than exposures observed at the same dose with SAGE-217 Oral Solution.

Neuroactive steroids are a class of endogenous and synthetic positive allosteric modulators that target both synaptic and extra-synaptic $GABA_A$ receptors (Belelli 2002 and confirmed in the Sponsor's in vitro studies). This diverse activity profile suggests that neuroactive steroid $GABA_A$ receptor-positive allosteric modulators could exhibit robust activity against essential tremor. Administration of SAGE-547 injection, a proprietary formulation of the endogenous neuroactive steroid, resulted in significant reductions in upper limb kinetic tremor scores compared to placebo in a Phase 2 proof-of-principle study (IND 122,280). Based on these results with SAGE-547, the study design for single-ascending dose study 217-CLP-101 included a cohort of subjects with essential tremor (N=6) who received SAGE-217 Oral Solution (55 mg) in an open-label manner. Data from this cohort indicate that single doses of SAGE-217 Oral Solution resulted in a reduction in the tremor symptoms, suggesting that SAGE-217 might be effective in treating PD.

There are no clinical efficacy data of SAGE-217 Oral Solution or Capsules in PD, since the present study is the first study in this indication.

5.4. Potential Risks and Benefits

Protocol 217-PRK-201 is the first clinical study evaluating the efficacy of SAGE-217 in PD. Thus, the potential benefits in this population are unknown, although the risks are likely to be similar to those mentioned in the Investigator's Brochure. GABA compounds that cross the blood-brain barrier or increase GABA activity alleviate muscle stiffness caused by a lack of GABAergic tone (Winkler 1999), validating this receptor as a therapeutic target. Given the promising clinical data with another neuroactive steroid (SAGE-547) in conjunction with the shared broad receptor selectivity profile, oral bioavailability, long half-life, preclinical evidence of anxiolytic activity, and safety data of SAGE-217, it is possible that patients may have a clinical benefit at the exposures selected for this study.

In the 217-CLP-103 study, SAGE-217 Capsules were found to be generally well-tolerated with no serious AEs reported during the treatment and follow-up periods. The most frequent AE observed was sedation that was mild, transient, and occurred within 1 to 4 hours following dosing and generally dissipated by 8 hours. The clinical portion of this study has recently completed; the final report is in progress.

In view of the few risks associated with administration of SAGE-217 that have been identified to date, intra-patient dose-reduction designs have been chosen for Part A and Part B to permit reduction in dose based on tolerability (adverse events), specifically sedation, versus treatment effect. In Part A, each subject will start with an initial dose of SAGE-217 Oral Solution, 30 mg; subjects unable to tolerate 30 mg will receive 20 mg; subjects unable to tolerate 20 mg will receive 10 mg. In Part B, each subject will receive SAGE-217 in the evening (PM) starting with an initial dose of SAGE-217 Capsules, 20 mg for two days; subjects able to tolerate 20 mg will receive 30 mg. If the subject is unable to tolerate 30 mg, the subject will receive 20 mg and continue for the remainder of the dosing period. Subjects who cannot tolerate the 20-mg dose at any time during Part B will be discontinued and replaced. The tolerated dose for each subject in Part A and Part B will be the dose taken on Day 7. Given the high medical need and potential for benefit in PD, there is a favorable benefit-risk evaluation to investigate SAGE-217 in PD.

In conclusion, selection criteria for the proposed study take into account the potential safety risks. Continuous safety monitoring, and the implementation of a formal dose-reduction and study drug discontinuation scheme also have the potential to mitigate risk. From a benefit/risk perspective, the appropriate measures are being taken in order to ensure the safety of the subjects who will be enrolled.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. 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 PD tremor symptoms.

6.2. 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.

6.3. Pharmacokinetic Objectives

The PK objective of Part A is:

- To assess the PK profile of SAGE-217 Oral Solution in plasma samples.

The PK objective of Part B is:

- To assess the PK profile of SAGE-217 Capsules utilizing a population PK approach.

6.4. Endpoints

6.4.1. Primary Endpoints

Part A:

- Frequency and severity of adverse events and changes 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 (SSS) score.

Part B:

- Improvement in PD tremor as assessed by changes in the MDS UPDRS Pa.ii II/ III tremor score (defined as the sum of MDS-UPDRS items 2.10, 3.15, 3.16, 3.17 and 3.18).

6.4.2. Secondary Endpoints

Part A:

- Improvement in PD motor symptoms as assessed by changes in the Movement Disorder Society-Unified Pai-Icinson's Disease Rating Scale (MDS-UPDRS) - Pa.ii III (Motor Examination) total score.

Part B:

- Improvement in PD motor symptoms as assessed by changes in the MDS-UPDRS - Pa.ii III total score.
- Improvement in PD nonmotor and motor aspects of experiences of daily living as assessed by the MDS-UPDRS - Pali I and Part II scores, respectively.
- Improvement in PD overall symptoms as assessed by changes in the MDS-UPDRS - Paiis I-IV total score.
- Frequency and severity of adverse events and changes in vital signs, clinical laboratory data, electrocai·diogram (ECG) parameters, and suicidal ideation using the Colllllllbia-Suicide Severity Rating Scale (C-SSRS).

6.4.3. Pharmacokinetic Endpoints

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

6.4.4. Exploratory Endpoints

I [redacted]

I [redacted]

I [redacted]

I [redacted]

I [redacted]

7. INVESTIGATIONAL PLAN

For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol.

7.1. Overall Study Design

This study is a two-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 Oral Solution for 4 days in 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 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 of SAGE-217 Oral Solution (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 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 morning with food, as outlined in Section 9.1.1. 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). 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 (e.g., 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 (i.e., those who do not

experience a severe adverse event 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 adverse event 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 outline in Section 9.1.2. 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.

The study designs of Part A and Part B are displayed in Figure 1 and Figure 2, respectively. Assessments will be performed periodically during the study as outlined in the Schedule of Events for Part A and Part B (Table 2 and Table 3, respectively).

7.2. Number of Subjects

Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A 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).

7.3. Treatment Assignment

SAGE-217 will be administered with food in Parts A and B. Food intake will be standardized as specified by the Sponsor. If subjects are taking antiparkinsonian agent(s), administration with or without food will be determined by the Investigator.

Parts A and B of the study are open-label. Dose reductions for lack of tolerability will be allowed during both parts of the study (Section 7.4).

7.4. Dose Adjustment Criteria

Dose reductions of SAGE-217 for lack of tolerability will be allowed during both parts of the study. If at any time the dose is not tolerated in Part A, as determined by the Investigator, the dose on the next day will be reduced to the next lowest dose (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). In Part B, subjects tolerating the initial 20-mg dose on Days 1 and 2 will receive a 30-mg dose on Day 3 and continue for the remainder of the dosing period. If on Day 3 or any time thereafter, the 30-mg dose is not tolerated, the dose on the next day must be reduced to 20 mg and continued for the remainder of the dosing period.

7.5. Criteria for Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons, including the occurrence of adverse events or other findings suggesting unacceptable risk to subjects, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their Institutional Review Board (IRB) and initiate withdrawal procedures for participating subjects.

Figure 1: Study Design of Part A

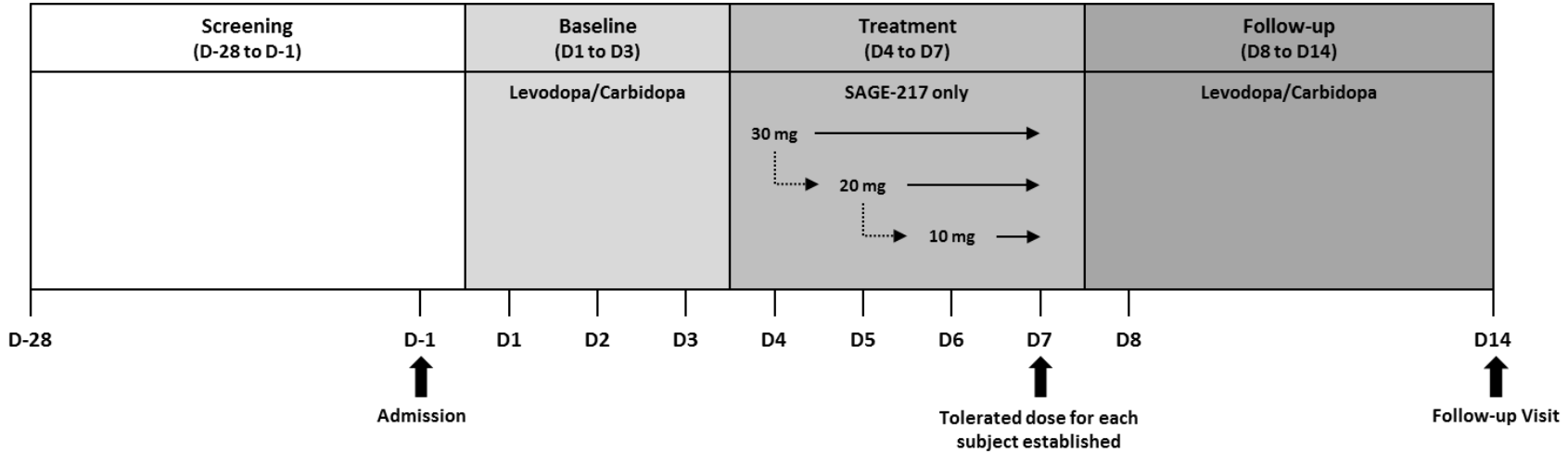
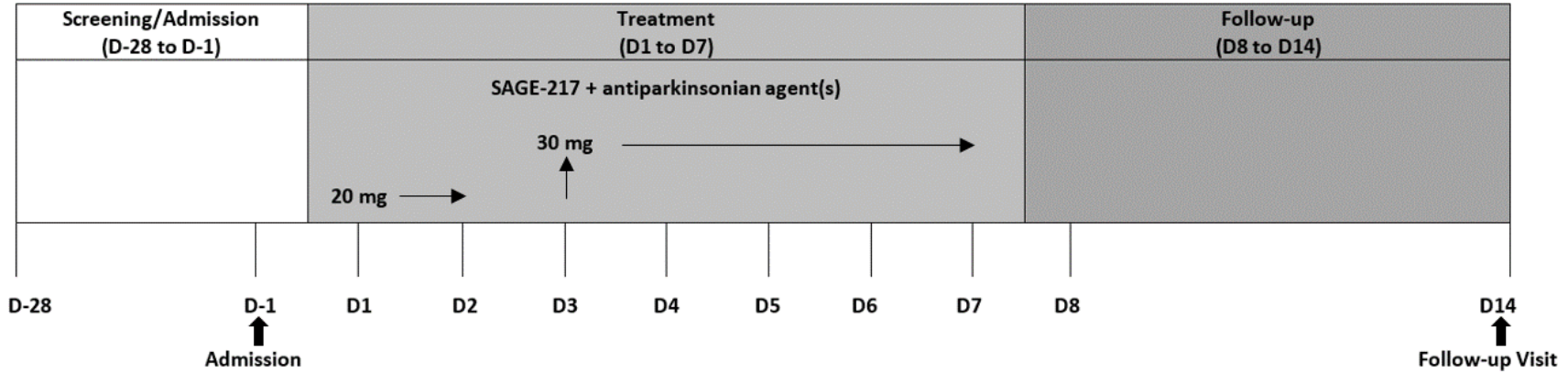


Figure 2: Study Design of Part B



NOTE: Part B will be initiated only after review of the Part A interim analysis (after 10 subjects have completed Part A).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Subjects must meet the following inclusion criteria for enrollment in the study:

1. Subject has signed an informed consent form (ICF) before any study-specific procedures are performed.
2. Subject is between 40 and 75 years of age, inclusive.
3. Subject has a diagnosis of idiopathic PD based on modified UK Brain Bank Criteria (modified to allow individuals with a family history of PD) (Hughes 1992; Appendix 1).
4. **Part A**: Subjects with PD with a duration of less than 7 years and must meet the criteria for Hoehn and Yahr stage 2 or stage 3 (Appendix 2).

   Part B: Subjects with PD and must meet the criteria for Hoehn and Yahr stage 1-4 (Appendix 2) assessed during the "on" period (assumed to be within 2 hours of dosing with antiparkinsonian agent(s)), and have a tremor with a MDS-UPDRS Part II/III tremor score of ≥8 (sum of items: 2.10, 3.15, 3.16, 3.17 and 3.18) AND a MDS-UPDRS item score ≥3 in at least one limb (from items 3.15, 3.16, or 3.17). Inclusion criteria tremor scores must be assessed during "on" periods during the screening and Day -1 visit.
5. **Part A**: Subject has a stable dose of antiparkinsonian agent(s) including immediate-release oral Levodopa or Carbidopa-Levodopa (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.

   Part B: Subject is receiving a stable dose of antiparkinsonian agent(s) (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.
6. **Part A only**: Subject is willing to discontinue his/her treatment with immediate-release oral Levodopa or Carbidopa-Levodopa for at least 8 hours prior to dosing with SAGE-217.
7. **Part A**: Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) or amantadine at least 5 days prior to the day of admission (Day -1).

   Part B: Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) by Day -6 or amantadine by Day -10.
8. Subjects taking an antidepressant drug, sleep medication, or neuroleptic must have been on a stable dose for at least 1 month prior to the baseline visit.
9. Subjects must have a MoCA score of >22.
10. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests.
11. **Part A**: Female subjects must agree to practice a highly effective method of birth control while on study through completion of the last follow-up visit. If a subject discontinues

early after receiving a dose of SAGE-217, then the subject must continue this method of birth control for at least 7 days following the last dose of study drug. Highly effective methods of birth control include combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, or sexual abstinence.

Part B: Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause) and/or surgically sterile:

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception
- associated with inhibition of ovulation.
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner.
- Sexual abstinence (no sexual intercourse).

12. Male subjects must agree to practice a highly effective method of birth control while on study, and for 13 weeks after receiving the last dose of study drug. Effective methods of birth control include sexual abstinence, vasectomy, or a condom with spermicide (men) in combination with their partner's highly effective method.
13. Males must be willing to abstain from sperm donation and females from donating eggs while on study through 13 weeks after receiving the last dose of study drug.
14. **Part B only**: Subjects who participated in Part A and meet all eligibility criteria for Part B must have tolerated at least 20 mg SAGE-217 in Part A, otherwise they are ineligible.

8.2. Subject Exclusion Criteria

Subjects who met any of the following exclusion criteria will be excluded from the study:

1. Subjects with a known hypersensitivity to SAGE-217 Oral Solution or its major excipient, HPβCD (**Part A**) or SAGE-217 Capsule or its excipients (**Part B**).
2. **Part A**: Subjects with early PD (Hoehn and Yahr stage 1) or advanced PD (Hoehn and Yahr stage 4 or stage 5).

   Part B: Subjects with advanced PD (Hoehn and Yahr stage 5).

3. Subjects with any medical or psychiatric condition that jeopardizes/compromises his/her ability for participation. This includes schizophrenia spectrum and other psychotic disorders, substance-related and addictive disorders, feeding and eating disorders, bipolar and related disorders, structural brain disease including but not limited to history of encephalitis or hydrocephalus and history of clinically significant stroke, or anticipating starting psychotherapy or behavior therapy during the course of the study, or who started psychotherapy or behavior therapy within 30 days prior to Day 1.
4. Subjects with a history of:
    a. Electroconvulsive therapy;
    b. Stereotaxic brain surgery (deep brain stimulation) for PD;
    c. History of suicide attempt within 2 years, or has answered YES to questions 3, 4, or 5 on the C-SSRS at the screening or Day -1 visits, or has current suicidal ideation; or
    d. Impulse control disorder.
5. **Part A only**: Subjects with severe depression as defined by a BDI-II score >19.
6. **Part B only**: Subject has recent exposure (14 days prior to the Day -1 visit) to tremorogenic drugs, as defined in Appendix 4.
7. Subjects with Type I or Type II diabetes mellitus.
8. Subjects with presence of drug-induced parkinsonism (eg, metoclopramide, flunarizine), metabolic identified neurogenetic disorders (eg, Wilson's disease), encephalitis, or other atypical Parkinsonian syndromes (eg, progressive supranuclear palsy, multiple system atrophy).
9. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.
10. Subject has clinically significant abnormal physical examination OR 12-lead ECG at the screening or admission visits. NOTE: QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study. ECG may be repeated once if initial values obtained are outside the specified limits.
11. Subject has a history, presence and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies 1 and 2.
12. Subject has exposure to another investigational medication or device within the prior 30 days.
13. Subject has donated one or more units of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing (1 unit = 450 mL).
14. Subject is unwilling or unable to comply with study procedures.
15. Subject has used any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit,

Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.

8.3. Subject Withdrawal Criteria

Participation in the study is strictly voluntary. Subjects are free to discontinue the study at any time without giving their reason(s).

A subject must be withdrawn from the study treatment in the event of any of the following:

- Withdrawal of the subject's consent;
- New onset of a condition that would have met exclusion criterion, is clinically relevant and affects the subject's safety, and discontinuation is considered necessary by the Investigators and/Sponsor;
- Occurrence of intolerable adverse events;
- Occurrence of pregnancy;
- Intake of nonpermitted concomitant medication;
- Subject noncompliance;
- Significant protocol deviation determined in consultation with the Medical Monitor.

If a subject fails to attend scheduled assessments during the course of the study, the Investigators must determine the reasons and the circumstances as completely and accurately as possible and document this in the subject's source documents.

Subjects may be withdrawn from the study if there is concern for the subject's safety or it is determined that the subject is no longer a qualified participant. Subjects who cannot tolerate the 10-mg dose at any time during Part A or the 20-mg dose at any time during Part B will be withdrawn. Any subject who is withdrawn from the study for any reason is to have the final visit assessments performed.

Subjects who withdraw or are withdrawn from the study may be replaced.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug Treatment

For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol. All doses of SAGE-217 (Oral Solution or Capsule) will be administered with food.

9.1.1. Part A

Subjects participating in Part A of the study will take SAGE-217 Oral Solution in an open-label manner. 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 the following 3 days (Days 1 to 3). On the morning of Day 4, subjects will stop their immediate-release oral Levodopa and take SAGE-217 for 4 days (Days 4 to 7) in the AM with food. On Day 4, subjects will receive a 30 mg dose of SAGE-217. Subjects not tolerating 30 mg will receive 20 mg the next day, and subjects not tolerating 20 mg will receive 10 mg the next day. 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. Levodopa treatment will be resumed on Day 8 and continue through Day 14.

9.1.2. Part B

Subjects participating in Part B of the study will take SAGE-217 Capsules in an open-label manner. Subjects on a stable dose of antiparkinsonian agent(s) will continue taking them for the duration of the study. All subjects will receive SAGE-217, 20 mg, at 8PM on Days 1 and 2. On Day 3, subjects tolerating the initial dose (i.e., those who do not experience a severe adverse event judged by the Investigator to be related to study drug) will receive a dose increase (SAGE-217, 30 mg), at 8PM, 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 adverse event 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.

9.2. Concomitant Medications

9.2.1. Prior/Concomitant Medications

Any concomitant medication determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study under the guidance outlined in Section 9.2.

Record the name, start date (if known), indication for use and whether ongoing or stopped of medications/treatments taken within 2 weeks prior to study entry as well as any medications taken during the study.

The charts of all study participants will be reviewed for new concomitant medications through discharge from the unit. Chart reviews will include examination of nursing and physician progress notes, vital signs, and medication records in order to identify adverse events that may be associated with new concomitant medications. New concomitant medications, ongoing concomitant medications with a change in dose, and medical procedures ordered (eg, laboratory assessments, computed tomography or magnetic resonance imaging scans) will be reviewed to determine if they are associated with an adverse event not previously identified.

The Investigator will document all doses of Levodopa and Carbidopa-Levodopa taken by the subject and the use of rescue medication.

9.2.2. Prohibited Medications

Subjects who have used any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug are to be excluded from the study; these medications/products are prohibited during the study.

The anticholinergic drug classes listed in Appendix 3 are not permitted in the 5 days prior to the admission visit (Day -1) of Part A and Part B. The list provides non-exhaustive examples of each drug class.

Amantadine is not permitted in the 5 days prior to the admission visit of Part A or 9 days prior to the admission visit of Part B.

The tremorogenic drugs listed in Appendix 4 are not permitted in the 14 days prior to the admission visit of Part B.

9.3. Treatment Compliance

Study drug (SAGE-217 Oral Solution or Capsule) will be prepared by the site pharmacist. All doses of study drug will be administered by site staff while the subject is confined to the clinical unit. The Investigator(s) or designee will record the time and dose of study drug administration in the source documents. Any reasons for noncompliance will also be documented, including:

- Missing visits;
- Interruptions in the schedule of administration; and
- Nonpermitted medications.

The time at which study procedures are conducted should follow the protocol timelines as closely as possible.

9.4. Randomization and Blinding

Not applicable; Part A and Part B of the study are open-label.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

10.1.1. SAGE-217 Oral Solution

SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dosages. The 6 mg/mL stock SAGE-217 Oral Solution will be compounded from SAGE-217 Drug Substance Powder in the Bottle and Excipient(s) in the Bottle (manufactured under current Good Manufacturing Practice [GMP] conditions [redacted]) and further admixed at the clinical site in preparation for dosing. Detailed instructions for study drug preparation will be provided in the Pharmacy Manual.

The Sponsor will not provide Levodopa or Carbidopa-Levodopa during the study; subjects will use their prescribed Levodopa or Carbidopa-Levodopa.

10.1.2. SAGE-217 Capsule

SAGE-217 Capsules are available as hard gelatin capsules containing a white to off-white powder. In addition to the specified amount of SAGE-217 Drug Substance, active SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients. Capsules will be available in 5-mg, 10-mg and 20-mg dose strengths. Subjects will be administered two capsules per dose. Detailed instructions for study drug preparation will be provided in the Pharmacy Manual.

10.2. Study Drug Packaging and Labeling

The composition and pharmaceutical quality of the investigational product will be maintained according to the current GMP and Good Clinical Practice (GCP) guidelines and available for review in the study medication documentation. SAGE-217 Oral Solution will be provided to the site as powder in the bottle and excipient(s) in the bottle units to be compounded in the pharmacy at a volume of 125 mL of a 6 mg/mL stock solution and then further diluted to approximately 40 mL at the identified doses. SAGE-217 Capsules will be provided to the site in appropriately labeled bottles. Study drug labels with all required information and conforming to all applicable Code of Federal Regulations and GMP/GCP guidelines will be prepared by the clinical research organization.

10.3. Study Drug Storage

Upon receipt of study drug (SAGE-217), the Investigator or designee will inspect the materials and complete and return the acknowledgment of receipt form enclosed with the parcel. A copy of the signed receipt will be kept in the study files.

The study drug materials for SAGE-217 Oral Solution must be carefully stored at the temperature specified in the Pharmacy Manual (eg, clinical dosing solutions stored at approximately 2 to 8°C for 11 days with 24 hours of room temperature excursions allowed after preparation), safely and separately from other drugs. SAGE-217 Capsules may be stored at room temperature.

The study drug may not be used for any purpose other than the present study. After the study is completed, all unused study drug must be retained, returned as directed, or destroyed on site per the Sponsor's instructions.

The Investigator or designee will be responsible for ensuring appropriate storage, compounding, dispensing, inventory, and accountability of all clinical supplies. An accurate, timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory must be available for inspection by the designated representatives of the Sponsor or the Sponsor's representatives on request, and must include the information below:

- The identification of the subject to whom the drug was dispensed;
- The date(s) and quantity of the drug dispensed to the subject; and
- The product lot/batch number.

The preparation of the study drugs must be documented on a 'Drug Preparation and Dispensing Log Form' or similar form.

A copy of the inventory record and a record of any clinical supplies that have been destroyed must be documented. This documentation must include at least the information below or as agreed with the Sponsor:

- The number of prepared units;
- The number of administered units;
- The number of unused units;
- The number of units destroyed at the end of the study;
- The date, method, and location of destruction.

10.4. Study Drug Preparation

Each bottle of SAGE-217 Oral Solution 6 mg/mL will be compounded at the clinical pharmacy from components manufactured [redacted] and supplied by the Sponsor per the directions provided in the Pharmacy Manual. The batch formula for a 125 mL solution of the 6 mg/mL stock solution is shown in Table 5.

Table 5: Batch Formula for 125 mL of Stock SAGE-217 Oral Solution 6 mg/mL

Ingredient	Compendia Specification	Concentration (mg/mL)	Amount (mg/Bottle)
SAGE-217	not applicable	6	750
HPβCD [redacted]	USP/EP	457	57,100
Sucralose	USP/NF	0.025	3.124
Water for Injection	USP	not applicable	85,650

Abbreviations: EP = European Pharmacopeia; HPβCD = hydroxypropyl-β-cyclodextrin; NF = National Formulary; USP = United States Pharmacopeia

For the capsule formulation, subjects will swallow two capsules per dose with food.

10.5. Administration

SAGE-217 will be administered with food in the morning in Part A and in the evening in Part B.

Doses of SAGE-217 Oral Solution will be prepared as an approximate 40 mL oral solution to be swallowed all at once, followed by approximately 200 mL of water that has been used to rinse the dosing bottle. The start time of swallowing the approximately 40 mL oral solution is time zero for all assessments. Subjects may have assistance from the clinic staff when taking the study drug.

During Confinement, each subject's antiparkinsonian agents, including Levodopa or Carbidopa-Levodopa, will be administered by site personnel according to the site's standard operating procedures.

10.6. Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator or designee must maintain a record of all study drug received, used, and discarded.

The Sponsor will be permitted access to the study supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

The Investigator will document all doses of Levodopa or Carbidopa-Levodopa taken by the subject, including rescue doses.

10.7. Study Drug Handling and Disposal

The pharmacist or designee for drug accountability is to document the date and time of initial compounding (oral solution only), subsequent admixture of dosing solutions (oral solution only), administration of study drug, and for which subject the study drug was intended (ie, record subject initials and birth date or other unique identifier).

At the end of the study, any unused study drug will be retained or returned to the Sponsor for destruction or destroyed locally per the Sponsor's directions; disposition of study drug will be documented.

11. ASSESSMENT OF EFFICACY

Efficacy assessments include evaluation of PD symptoms by the MDS-UPDRS, [redacted] Assessments will be perfo1med periodicall y dming the study as outlined in the Schedule of Events for Pali A and Pali B (Table 2 and Table 3, respectively).

11.1. Movement Disorder Society- Unified Parkinson's Disease Rating Scale

The UPDRS is the most commonly used scale in clinical studies of PD (Ramaker 2002). In 2007, the MDS revised the scale, which was known as the MDS-UPDRS (Goetz 2007), and subsequently demonstrated the validity of the MDS-UPDRS for rating PD (Goetz 2008). The modified UPDRS includes fom scales, with various subscales. Each item is rated from 0 (no1m al) to 4 (severe) (Table 6). The fom MDS-UPDRS scales are:

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

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

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

Pait IV: Motor complications (6 items)

Table 6: Rating Scale for the MDS-UPDRS

Rating	Description
O = n 01mal	No symptoms /signs
1 = sligh t	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

Several questions in Pait I and all questions in Pait II can be answered by the patient/caregiver and completed without the Investigator's input. The remaining questions in Part I that deal with complex behaviors, the objective assessments of parkinsonism (Pait III), and the questions that deal with motor fluctuations and dyskinesias (Pait IV) ai·e co mpleted by In vestigator interview. The tim e requ ired for ad m inistering the MDS-UPDRS is estimated to be less than 10 minutes for the interview items of Pait I, 15 minutes for Pait III, and 5 minutes for Paii IV (Goetz 2008).
The complete MDS-UPDRS is to be administered in Pait A at screening, Admission (Day -1), on Day 8 prior to resuming Levodopa, and on Day 14. The complete MDS-UPDRS is to be administered in Pait B at screening, Admission (Day -1), in the morning of Days 1 and 8, and on Day 14. In both Paits A and B, the Admission (Day -1) complete MDS-UPDRS is perfo1med only if the time between Screening and Admission is ?:.7 days; othe1wise, the MDS-UPDRS Pait III only (Pait A) or Pait II and Pait III (Pait B) are perfo1med.

Pait II of the MDS-UPDRS assesses 13 categories of motor experiences of daily living: speech, salivation and drooling, chewing and swallowing, eating tasks, dressing, hygiene, handwriting,

doing hobbies and other activities, turning in bed, tremor, getting out of bed, car, or deep chair, walking and balance, and freezing (Goetz, 2008). Part II of the MDS-UPDRS (motor examination) is to be completed in Part B at 12 and 23 hours postdose on Days 1, 2, 3, 4, 5, and 6. If the complete MDS-UPDRS is not performed on Admission due to Admission taking place <7 days after Screening, then Part II should also take place on Admission (Day -1) for Part B.

Part III of the MDS-UPDRS 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, global spontaneity of movement (Goetz, 2008). Part III of the MDS-UPDRS (motor examination) is to be completed in Part A at 2, 4, 8, and 12 hours postdose on Days 1, 2, 3, 4, 5, 6, and 7. MDS-UPDRS is to be assessed within ±10 minutes of the scheduled times through the 4-hour time point and within ±15 minutes of the scheduled times for the 6-hour through 12-hour time points. Part III of the MDS-UPDRS (motor examination) is to be completed in Part B at 12 and 23 hours postdose on Days 1, 2, 3, 4, 5, and 6. If the complete MDS-UPDRS is not performed on Admission due to Admission taking place <7 days after Screening, then Part III should also take place on Admission (Day -1) for both Parts A and B.

All MDS-UPDRS measurements in Part B should be taken during the "on" period (within 2 hours of dosing with antiparkinsonian agent(s)).

The MDS-UPDRS is provided in Appendix 5.

11.2. Exploratory Endpoints

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

12. PHARMACOKINETICS

12.1. Blood Sample Collection

In Part A, plasma samples for PK analysis will be collected predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Day 4; predose on Day 5 and Day 6; predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Day 7; in AM of Day 8; and Day 14. Samples are to be collected within ±5 minutes of the scheduled sampling time.

In Part B, plasma samples for PK analysis will be collected predose and 13 hours postdose on Day 1; and 13 hours postdose on Days 2 through 7, and on Day 14. Samples are to be collected within ±1 hour of the scheduled sampling time.

The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. The Investigator or designee will arrange to have the plasma samples processed, stored, and transported as directed for bioanalysis.

An additional PK sample may be collected at any time if clinically indicated and at the discretion of the Investigator (eg, for unusual or severe adverse events).

Each sample will be marked with unique identifiers such as the study number, subject number, and the nominal sample time. The date and actual time that the blood sample was taken will be recorded on the eCRF or electronically with a bar code or other method.

12.2. Storage and Shipment of Pharmacokinetic Samples

The plasma samples should be kept frozen at approximately -70 to -80°C until analyzed. They should be packed as directed to avoid breakage during transit and with sufficient dry ice to prevent thawing for at least 72 hours. A specimen-identification form must be completed and sent to the laboratory with each set of samples. The clinical site will arrange to have the plasma samples transported as directed for bioanalysis as detailed in the PK instructions.

12.3. Sample Analysis

Bioanalysis of plasma samples for the determination of concentrations of SAGE-217 and possibly SAGE-217 metabolites will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory. Pharmacokinetic parameters will be derived such as area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), the distributional half-life and terminal half-life ($t_{½}$), and steady-state drug concentration in the plasma (C_{ss}).

13. ASSESSMENT OF SAFETY

13.1. Safety and Tolerability Parameters

Safety and tolerability of study drug will be evaluated by adverse event reporting, vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, and SSS (Part A only) and MOAA/S (Part A only) scores.

13.1.1. Demographic/Medical History

Age, gender, race, and ethnic origin will be recorded at the Screening visits. A full medical history, including PD history (e.g., time of diagnosis, Hoehn and Yahr staging) and medication history, will be recorded at the Screening visits.

13.1.2. Vital Signs

Vital signs comprise respiratory rate, temperature, and supine (supine for at least 5 minutes prior to the measurement) and standing systolic and diastolic blood pressure and heart rate.

In Part A, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in AM of Day 8; and on Day 14. Vital signs and pulse oximetry are to be assessed within
±10 minutes of the scheduled times through the 4-hour time point and within ±15 minutes of the scheduled times for the 6-hour through 16-hour time points.

In Part B, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, and 12 hours postdose on Days 1 through 7; and on Day 14. Vital signs and pulse oximetry are to be assessed within ±10 minutes of the 1- and 2-hour time points and within ±15 minutes of the 12-hour time point.

13.1.3. Weight and Height

Body weight and height will be measured at the Screening visits for Parts A and B.

13.1.4. Physical Examination

A physical examination of all major body systems will be undertaken and recorded at the Screening visits for Parts A and B. Symptom-directed physical examinations will be performed during Part A on Admission (Day -1), Day 1, Day 3, Day 4, Day 6, and Day 8. Symptom-directed physical examinations will be performed during Part B on Admission (Day -1), Day 1, Day 3, Day 4, Day 6, and Day 8.

13.1.5. Electrocardiogram (ECG)

A supine 12-lead ECG will be performed at the times specified below and the standard intervals recorded as well as any abnormalities.

In Part A, the 12-lead ECG will be assessed at screening and Admission (Day -1); predose on Days 1 and 3; predose and 1 and 12 hours postdose on Days 4, 5, 6, and 7; in AM on Day 8; and

Day 14. In Part B, the 12-lead ECG will be assessed at screening and Admission (Day -1); predose and 1 and 12 hours postdose on Days 1, 3, 5, and 7, and on Day 14.

All time points are relative to the time of dosing. ECGs are to be performed within ±10 minutes of the predose and 1-hour time points and within ±15 minutes of the 12-hour time point.

13.1.6. Laboratory Assessments

In Part A, blood samples will be collected for hematology and serum chemistry at the Screening visit, on Admission (Day -1), predose on Days 4, 6, and 8; and on Day 14. Urine samples will be collected in Part A at screening and Admission (Day -1); predose on Day 4 and Day 7; and on Day 14. In Part B, blood and urine samples will be collected at screening and Admission (Day -1); predose on Days 4 and 6; and on Day 8 and Day 14. On Day -1 of Part B, two blood samples will be taken: one sample will be sent to the central lab to be analyzed for reporting purposes and one sample is to be analyzed locally for study eligibility with regard to hematology/serum chemistry criteria.

Serum and urine samples for pregnancy tests (females only) will also be collected. These assessments should be performed in accordance with the Schedule of Events (Table 2 and Table 3 as outlined individually below.

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS). Screening results considered abnormal, CS recorded at the Screening visit may make the subject ineligible for the study pending review by the Medical Monitor. Clinical laboratory results that are abnormal, CS during the study but within normal range at baseline and/or indicate a worsening from baseline will be considered adverse events, assessed according to Section 13.2, and recorded in the eCRF.

13.1.6.1. Hematology

Hematology tests will include complete blood count (CBC), including red blood cells, white blood cells with differentiation, hemoglobin, hematocrit, reticulocytes, and platelets. The coagulation panel will include activated partial thromboplastin time, prothrombin time, and international normalized ratio.

13.1.6.2. Blood Chemistry

Serum chemistry tests will include serum electrolytes, renal function tests, including creatinine, blood urea nitrogen, bicarbonate or total carbon dioxide, liver function tests, including total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), alkaline phosphatase (Part B only), total protein, and albumin.

13.1.6.3. Urinalysis

Urinalysis will include assessment of protein, blood, glucose, ketones, bile, urobilinogen, hemoglobin, leukocyte esterase, nitrites, color, turbidity, pH, and specific gravity.

13.1.6.4. Virus Serology

Subjects will be screened for hepatitis (HBsAg and anti-HCV) and HIV prior to being enrolled in the study.

13.1.6.5. Pregnancy Screen

Females of childbearing potential will be tested for pregnancy at Parts A and B by serum pregnancy test at the Screening visits and by urine pregnancy test on Day -1 (Admissions). For Part B, females of childbearing potential will also be tested for pregnancy by urine pregnancy test at the follow-up visit on Day 14.

13.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS)

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

If in the opinion of the Investigator, the subject is showing any suicidal tendency, no further study drug will be administered and the subject will be referred to a psychologist or psychiatrist for further evaluation. This information will be tracked.

The "Baseline/Screening" C-SSRS form will be completed on Screening of Parts A and B (lifetime history and past 24 months). In Part A, the "Since Last Visit" C-SSRS form will be completed on Admission (Day -1); 12 hours postdose on Days 1, 2, and 3; predose on Days 4, 5, 6, and 7; and on Days 8 and 14. In Part B, the "Since Last Visit" C-SSRS form will be completed on Admission (Day -1); predose and 12 hours postdose on Day 1; 12 hours postdose on Days 2 through Day 7; and on Day 14. The C-SSRS is provided in Appendix 10.

13.1.8. Stanford Sleepiness Scale (SSS)

The SSS is 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'.

In Part A, the SSS will be administered on Admission (Day -1); predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in the AM on Day 8; and Day 14. All time points are relative to the time of dosing. 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. The SSS should be performed prior to the MOAA/S score. The SSS will not be administered in Part B. The SSS is provided in Appendix 11.

13.1.9. Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S)

The MOAA/S allows exploration of deeper sedation states than the SSS. If an 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. In Part A, the MOAA/S assessment should be

conducted after other assessments that are scheduled at the same time point. In Part A, the MOAA/S will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 3, 4, 5, 6, and 7; in AM on Day 8; and Day 14. The MOAA/S will not be performed in Part B. The MOAA/S is provided in Appendix 12.

13.2. Adverse and Serious Adverse Events

Adverse events will be collected after the ICF has been signed. Medical conditions that occur after the ICF has been signed will be captured on the adverse event eCRF.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (version 18.1 or higher).

13.2.1. Definition of Adverse Events

13.2.1.1. Adverse Event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an adverse event can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All adverse events that occur after any subject has been enrolled, before treatment, during treatment, or following the cessation of treatment until the Day 14 Follow-up visit of Parts A and B, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics.

13.2.1.2. Suspected Adverse Reaction

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

13.2.1.3. Serious Adverse Event

A serious adverse event is an adverse event occurring during any study phase and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- It results in death
- It is immediately life-threatening
- It requires inpatient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- It results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

All serious adverse events that occur after any subject has been enrolled, before treatment, during treatment, and until the Day 14 Follow-up visit of Parts A and B, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics.

13.2.1.4. Recording Sedation as an Adverse Event

In Part A and Part B, sedation will be recorded as an adverse event. Consideration should be given to the most appropriate term to describe the sedation characteristics.

For Part A, in order to standardize the reporting of sedation as adverse events, Investigators must record sedation as an adverse event if there is a score of >5 on the SSS and/or a score of ≤2 on the MOAA/S. SSS and MOAA/S do not apply to Part B.

13.2.2. Pregnancy

Any pregnancy occurring during this study will be reported within 24 hours of notification of the Investigator. The Investigator will promptly notify the Medical Monitor and withdraw the subject from the study. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The Investigator should request permission to contact the subject, the subject's spouse/partner (if the subject is male and his spouse/partner becomes pregnant) or the obstetrician for information about the outcome of the pregnancy (spontaneous miscarriage, elective termination, live birth), and in the case of a live birth, about any congenital abnormalities. If a congenital abnormality is reported, then it should be recorded in the source documents and reported as a serious adverse event. Spontaneous miscarriages should also be reported and handled as serious adverse events. Elective abortions without complications should not be handled as adverse events.

13.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each adverse event (unrelated, possibly related or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the adverse event should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the adverse event, then the adverse event should be considered "related."

Not related	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possibly related	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.
Probably related	The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.

If the relationship between the adverse event/serious adverse event and the investigational product is determined to be "possible" or "probable", the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

13.4. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as adverse events unless they prompt corrective medical action by the Investigator, constitute a serious adverse event or lead to discontinuation of administration of study drug.

Information about adverse events will be collected from the signing of the ICF until the final visit of the study for that subject. Adverse events that occur after the first administration of study drug will be denoted TEAEs.

All adverse events will be followed until they are resolved or have reached a clinical plateau with no expectation of future change.

The adverse event term should be reported in standard medical terminology when possible. For each adverse event, the Investigator will evaluate and report the onset (date and time), resolution or clinical plateau (date and time), intensity, causality, action taken, outcome, and whether or not it caused the subject to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe adverse events. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.2.1.3. An adverse event of severe intensity may not be considered serious.

13.5. Reporting Serious Adverse Events

All serious adverse events (regardless of causality) will be recorded from the signing of the ICF until the Day 14 Follow-up visit of Parts A and B. Any serious adverse events considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All serious adverse events must be reported to the Sponsor or Sponsor's designee immediately by phone and in writing within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the serious adverse event pages, verify the accuracy of the information recorded on the serious adverse event pages with the corresponding source documents, and send a copy to Sage Therapeutics or designee.

Additional follow-up information, if required or available, should be sent to Sage Therapeutics or designee within 24 hours of receipt; a follow-up serious adverse event form should be completed and placed with the original serious adverse event information and kept with the appropriate section of the CRF and/or study file.

Sage Therapeutics or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB of all serious adverse events that occur at his or her site if applicable per the IRB's requirements. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB of these additional serious adverse events.

14. STATISTICAL METHODS AND CONSIDERATIONS

14.1. Data Analysis Sets

The safety population is defined as all subjects who are administered at least one dose of study drug. Safety population will be used to provide descriptive summaries of all safety data.

The efficacy population will consist of all subjects in the safety population who receive at least one dose of study drug and have at least one postdose MDS-UPDRS evaluation. The efficacy population will be used to analyze all efficacy data.

The PK population will consist of all subjects in the safety population with sufficient plasma concentrations for PK evaluations.

Separate populations will be defined for each part of the study.

14.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. No imputation process will be used to estimate missing data. No sensitivity analysis of missing data will be performed.

14.3. General Considerations

For the purpose of all safety, efficacy, and exploratory analyses where applicable, baseline is defined as the last measurement prior to the start of study drug administration. Continuous endpoints will be summarized with n, mean, standard deviation (SD), median, minimum and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

14.4. Demographics and Baseline Characteristics

Demographics, such as age, gender, race, and ethnicity, and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized.

Categorical summaries, such as gender and race, will be summarized by frequency and percentage. Continuous summaries, such as age, height, weight, BMI, and baseline vital signs, will be summarized using descriptive statistics.

Hepatitis, 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 by subject.

14.5. Efficacy Endpoints

The primary endpoints of Part A relate to safety and tolerability. The primary endpoint for Part B is to evaluate the improvement in PD tremor as assessed by changes in the 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).

14.5.1. Secondary Efficacy Endpoints

fu Pait A, changes in the MDS-UPDRS- Pait III score will be Sllilllllaii·zed overall and by tolerated dose. fu Pait B, MDS-UPDRS Pali III total score, and the MDS-UPDRS - Pa.it s I- IV total score will be smmnai·ized overall and by and tolerated dose.

14.5.2. Exploratory Efficacy Endpoints

[redacted]

14.6. Safety and Tolerability Analyses

Data from vital signs, clinical laboratory measures, ECG, C-SSRS, SSS (Pa.ii A onl y), and MOAAIS (Pa1i A only) will be smnmai·ized using descriptive statistics by group and time point, where applicable. Continuous endpoints will be Sllilllllai·izedwith nllllber (n), mean, standai·d deviation, median, minimllllll, and maximllllll. fu addition, change from baseline values will be calculated at each time point and will be smmnai·ized using descriptive statistics. Out-of-range safety endpoints may be categorized as low or high, where applicable. For all categorical endpoints, sUilllna ries wi ll include counts and percentages.

14.6.1. Adverse Events

Adverse events will be coded using the MedDRA coding system (version 18.1 or higher). The analysis of adverse events will be based on the concept of TEAEs. A TEAE is defined as an adverse event with onset after the start of open-label study drng, or any worsening of a pre-existing medical condition/adverseevent with onset after the strut of ope n-l abe l study diu g and until 14 days after the last dose. The incidence of TEAEs will be sUillln ai·ized overall and by MedDRA System Organ Class, preferred tenn, and dose group. fucidences will be presented in order of decreasing frequency. fu addition, Sllilllllaii·es will be provided by maximllllll severity (see Section 13.4) and relationship to study diug (see Section 13.3).

Treatment-emergent adverse events leading to discontinuation and serious adverse events (see Section 13.2.1.3 for definition) with onset after the first dose of open-label study diug will also be sUillillaii·zed.

All adverse events and serious adverse events (including those with onset or worsening before the staii of open-label study diug) through the Day 14 Follow-up visit of Paii s A and B will be listed.

14.6.2. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from baseline of Pa.ii A and Pait B in vital signs will be evaluated by time point.

14.6.3. Physical Examinations

Screening physical examination results for Part A and Part B will be listed by subject. Any clinically significant physical examination will be recorded in medical history. Physical examination findings will be listed by subject and visit; abnormal findings will be flagged on the listing.

14.6.4. 12-Lead ECG

The following ECG parameters will be listed for each subject: heart rate, PR, QRS, QT, QTc, and QTcF. Any clinically significant abnormalities or changes in ECGs should be listed as an adverse event. Electrocardiogram findings will be listed by subject and visit.

14.6.5. Clinical Laboratory Evaluations

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline of Parts A and B in clinical laboratory measures will be summarized.

14.6.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality data collected on the C-SSRS will be listed for all subjects. Listings will include behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

14.6.7. Stanford Sleepiness Scale (SSS)

Sedation data collected on the SSS will be listed for all subjects in Part A. Changes in score over time will be represented graphically, and change from baseline of Part A will be summarized.

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

Sedation data collected on the MOAA/S will be listed for all subjects in Part A. Changes in score over time will be represented graphically, and change from baseline of Part A will be summarized.

14.6.9. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and will be coded using World Health Organization (WHO)-Drug dictionary September 2015, or later.

Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those taken during the 4 weeks prior to the date of the first dose of open-label study drug. Concomitant medications are defined as those with a start date on or after the first dose of open-label study drug, or those 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. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant. Details of prior and concomitant medications will be listed by study part, subject, start date, and verbatim term.

The use of rescue medication will be recorded and summarized.

14.7. Pharmacokinetic Analysis

Phaimacokinetic parameters will be Sllllirni.rized u s in g appropriate descriptive statistics. Time to reach maximllll concentration (tma.x) will be summarized using number (n), mean, standai·d deviation, median, minimllll, and maximllll. All other PK pai·ameters will be Sllillllarized using n, geometric mean, coefficient of vaii·ation, median, minimum, and maximllll and listed by subject.

Wherever necessaiy and appropriate, PK pai·ainetes will be dose-adjusted to account for individual differences in dose.

[redacted] Additional exposure-response analyses may be perfo1med for other measures of efficacy and safety.

14.8. Determination of Sample Size

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

14.9. Changes From Protocol Specified Analyses

Any changes from the analytical methods outlined in the protocol will be documented in the final statistical analysis plan.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of <Sponsor> will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sage Therapeutics or designee or its representatives. This will be documented in a Clinical Study Agreement between Sage Therapeutics and the Investigator.

During the study, a monitor from Sage Therapeutics or designee will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s);
- Confirm that facilities remain acceptable;
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts);
- Record and report any protocol deviations not previously sent to Sage Therapeutics or designee; and
- Confirm adverse events and serious adverse events have been properly documented on eCRFs and confirm any serious adverse events have been forwarded to Sage Therapeutics or designee and those serious adverse events that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

15.2. Audits and Inspections

Authorized representatives of Sage Therapeutics, a regulatory authority, an Independent Ethics Committee (IEC) or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sage Therapeutics or designee audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Council on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency about an inspection.

15.3. Institutional Review Board (IRB)

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator and institution will permit study-related monitoring, audits, IRB review, and regulatory inspections as requested by Food and Drug Administration, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (ie, original medical records, laboratory reports, hospital documents, progress reports, signed ICFs) in addition to eCRFs.

Quality assurance and quality-control systems with written standard operating procedures will be followed to ensure this study will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality-assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements made by the Sponsor with the Investigator/institution and any other parties involved with the clinical study will be in writing in a separate agreement.

17. ETHICS

17.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Sage Therapeutics or designee before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Sage Therapeutics or designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

17.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and the most recent amendment (2008) and are consistent with ICH/GCP and other applicable regulatory requirements.

17.3. Written Informed Consent

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

18. DATA HANDLING AND RECORDKEEPING

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

Electronic case report forms will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, and subject status.

The Investigator will have access to the electronic data capture system and will receive a copy of the subject eCRF data at the end of the study. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

18.1. Inspection of Records

Sage Therapeutics or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

18.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Sage Therapeutics or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18.3. Confidentiality

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available study registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used

towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

19. PUBLICATION POLICY

All information concerning SAGE-217 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

20. LIST OF REFERENCES

Belelli D, Casula A, Ling A, Lambert JJ. The influence of subunit composition on the interaction of neurosteroids with GABA(A) receptors. Neurophan nacology. 2002 Sep;43(4):651- 61.

[redacted]

Bergman H, Deuschl G. Pathophysiology of Parkinson's disease: from clinical neurology to basic neuroscience and back. Mov Disord. 2002;17:S28-S40.

[redacted]

di Michele F, Longone P, Romeo E, et al. Decreased plasma and cerebrospinal fluid content of neuroactive steroids in Parkinson's disease. Neurol Sci. 2003;24(3):172-3.

Goetz CG, Fahn S, Maitinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, fonnat, and clinimetric testing plan. Mov Disord. 2007;22(1):41-4 .

Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Pai·kinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov Disord. 2008;23(15):2129-70.

Hoehn M, Yahr M. Parkinsonism: onset, progression and mo1tality. Neurology. 1967;17(5):427-42.

[redacted]

Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Pai·kinson's disease. A clinico-pathological study of 100 cases. JNNP. 1992;55:181-4.

Jankovic J. Moto r fluctuations and dyskinesia in Parkinson's disease: Clinical manifestations. Mov Disord. 2005;11:ll -6.

Jankovic J. Parkinson's' disease: clinical features and diagnosis. JNNP. 2008;79:368-76.

Kasten M, Brnggemann N, Schmidt A, Klein C. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology. 2010;75 (5):478-9.

[redacted]

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatiy. 2011;168(12):1266-77.

Ramaker C, Marinus J, Stiggelbout AM, et al. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. Mov Disord. 2002;17(5):867- 76.

Siderowf A, Lang AE. Pre-motor Parkinson's disease; concepts and definitions. Mov. Disord 2012;27, 608-16.

Stem MB. Dopamine agonists modify the course of Parkinson disease. Arch Neurol. 2004;61:1969-71.

Weiner WJ. Initial treatment of Parkinson disease: levodopa or dopamine agonists. Arch Neurol. 2004;61:1966-9.

Winkler C, Bentlage C, Nikkhah G, et al. Intracranial transplants of GABA-rich striatal tissue induce behavioral recovely in the rat Parkinson model and promote the effects obtained by intrastriatal dopaminergic transplants. Exp. Neurol. 1999;155:165-186.

21. APPENDICES

Copies of scales and questionnaires included in the following appendices are for reference only; the rating scales and questionnaires reproduced in the eCRFs are to be used for actual subject assessment per the Schedule of Events.

APPENDIX 1. UNITED KINGDOM BRAIN BANK CRITERIA

UK PARKINSON'S DISEASE SOCIETY BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA*

Step 1. Diagnosis of Parkinsonian Syndrome

- Bradykinesia
- At least one of the following
  - Muscular rigidity
  - 4-6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease

- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

**From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181-184.*

APPENDIX 2. HOEHN AND YAHR STAGING CRITERIA

The Hoehn and Yahr scale, a commonly used system for describing how the symptoms of Parkinson's disease progress, was first published in 1967 (Hoehn 1967). The original scale included 5 disease stages, numbered 1 to 5.

Original Hoehn and Yahr Scale

Stage 1	Unilateral involvement only, usually with minimal or no functional disability
Stage 2	Bilateral or midline involvement without impairment of balance
Stage 3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent
Stage 4	Severely disabling disease; still able to walk or stand unassisted
Stage 5	Confinement to bed or wheelchair unless aided

APPENDIX 3. ANTICHOLINERGIC DRUGS

The following drugs are not permitted in the 5 days prior to receiving the first dose of study drug in Part A and Part B. The list below gives a non-exhaustive list of examples of each drug class.

A. Antimuscarinic agents

Atropine	Benzatropine	Biperiden	Chlorpheniramine
Dicyclomine	Dimenhydrinate	Diphenhydramine	Doxepin
Doxylamine	Glycopyrrolate	Hydroxyzine	Ipratropium
Orphenadrine	Oxitropium	Oxybutynin	Tolterodine
Tiotropium	Trihexyphenidyl	Scopolamine	Solifenacin
Tropicamide			

Tricyclic antidepressants (amitriptyline, clomipramine, doxepin, imipramine, trimipramine, amoxapine, desipramine, nortriptyline, protriptyline)

B. Antinicotinic agents:

Bupropion	Dextromethorphan	Doxacurium	Hexamethonium
Mecamylamine	Tubocurarine		

APPENDIX 4. TREMOROGENIC DRUGS

The following drug classes are not permitted in the 14 days prior to the Day -1 visit and for the duration of the study (up to the Day 14 visit). The list below gives a non-exhaustive list of examples of each drug class.

Anti-arrhythmics
amiodarone, procainamide

Antiepileptic drugs
valproic acid, carbamazepine

Antipsychotic agents
haloperidol, trifluoperazine

Antimanic agents/mood stabilizer
lithium at toxic levels

Antivirals
acyclovir, vidarabine

Beta adrenergic agonists
albuterol, terbutaline

Calcium Channel blockers
verapamil

CNS stimulants
methylphenidate, amphetamines, cocaine

Corticosteroids (local injection topical, or inhalation allowed)
cortisone, hydrocortisone, prednisone

Cytotoxic agents
cytarabine

Hormones
calcitonin, levothyroxine (levothyroxine is allowed if on a stable dose and euythroid)

Immunomodulatory
thalidomide

Immunosuppressants
cyclosporine, tacrolimus

Monoamine depleting agents
tetrabenazine

Oral hypoglycemic agents
metformin, glyburide, glipizide, tolbutamide, pioglitazone, rosiglitazone, acarbose, miglitol

Prokinetics
metoclopramide

Tricyclic antidepressants
amitriptyline, clomipramine, doxepin, imipramine, trimipramine, amoxapine, desipramine, nortriptyline, protriptyline

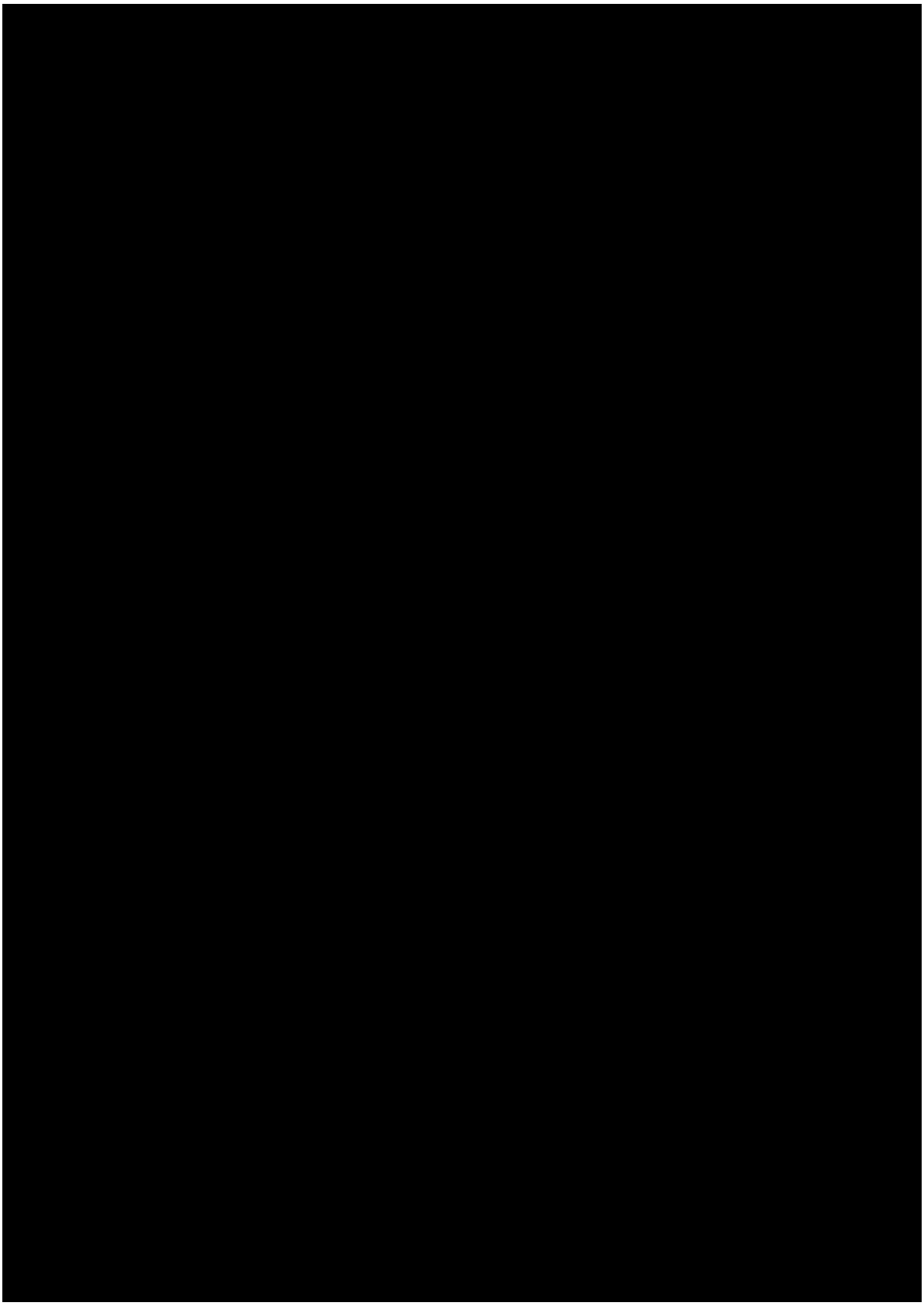
Selective Serotonin Reuptake Inhibitors (SSRIs)
fluoxetine (other SSRIs are allowed)

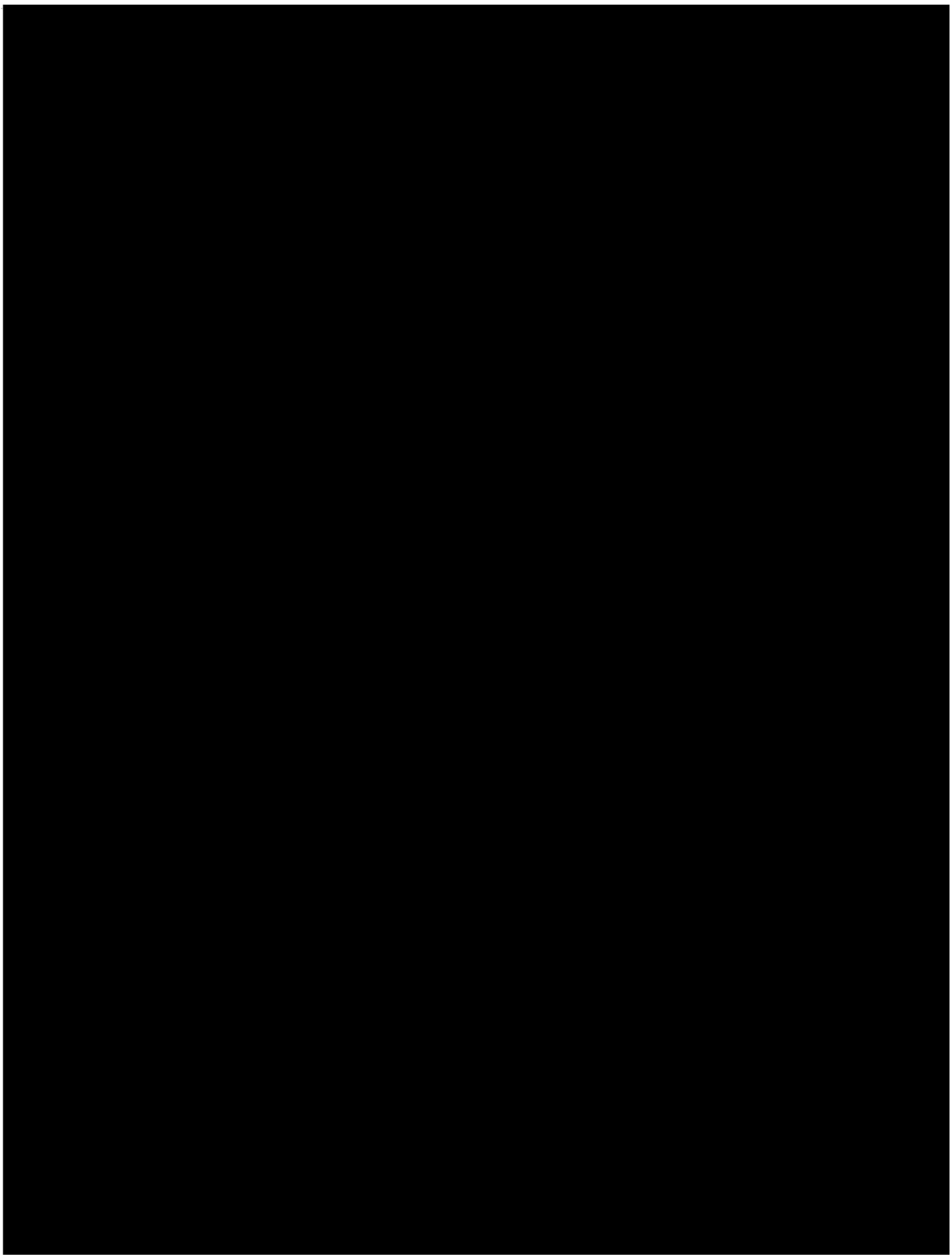
Statins
atorvastatin (other statins are allowed)

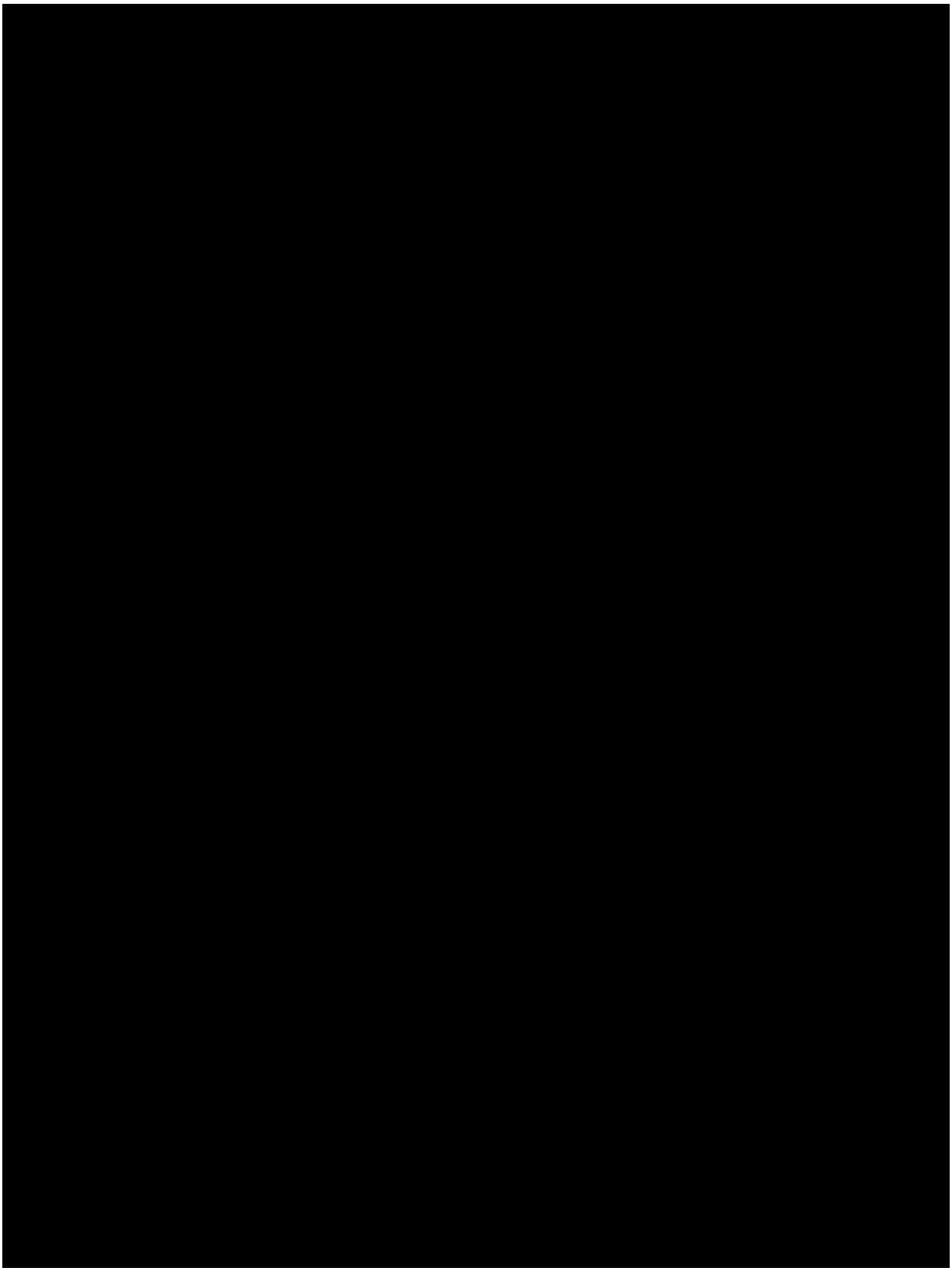
Sympathomimetics
epinephrine, pseudoephedrine
Weight loss medication
tiratricol
Xanthine derivatives
theophylline (caffeine/coffee and theophylline/theobromine/tea require a washout, cocoa beans are acceptable)

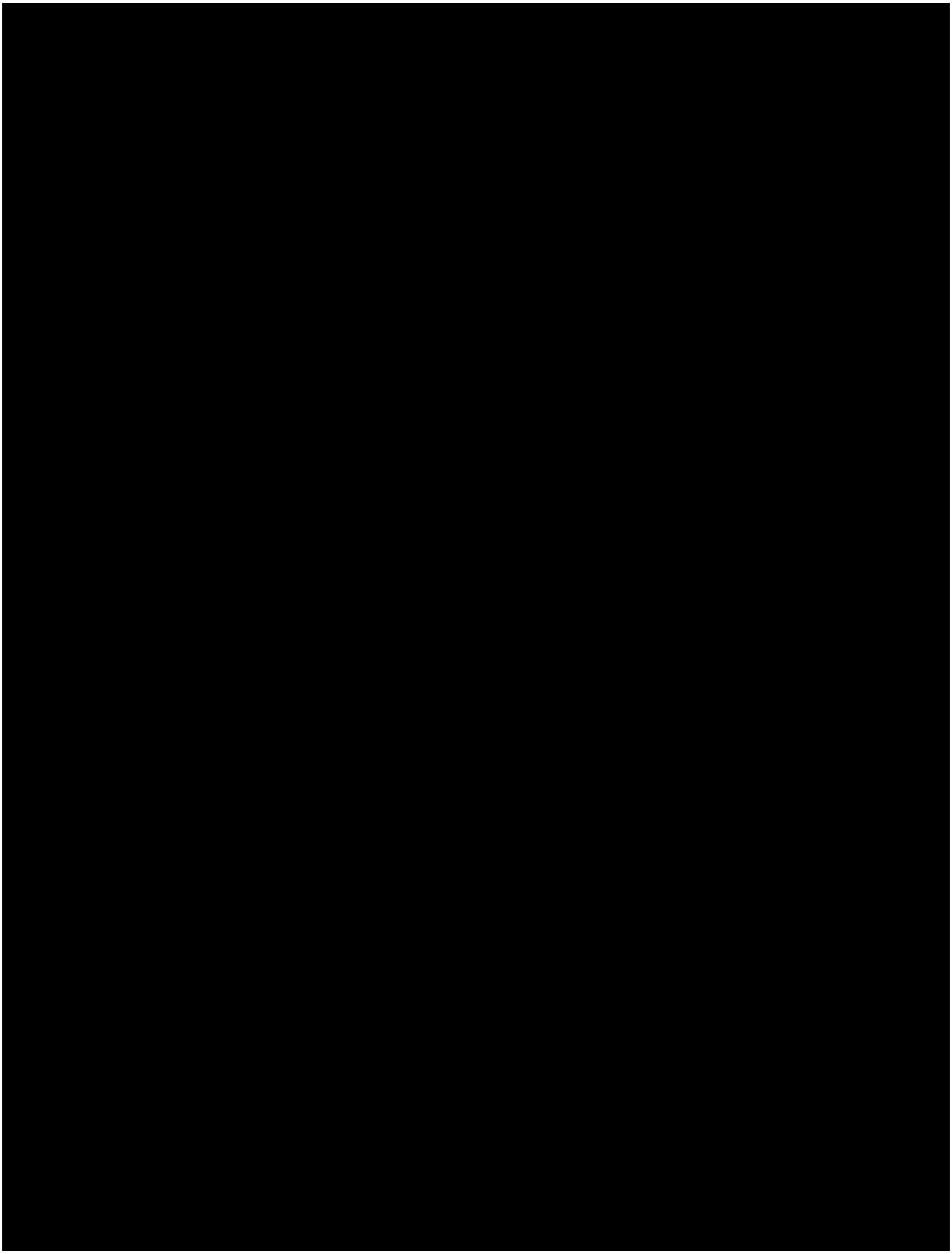
APPENDIX 5. MOVEMENT DISORDER SOCIETY-UNIFIED PARKINSON'S DISEASE RATING SCALE (MDS-UPDRS)

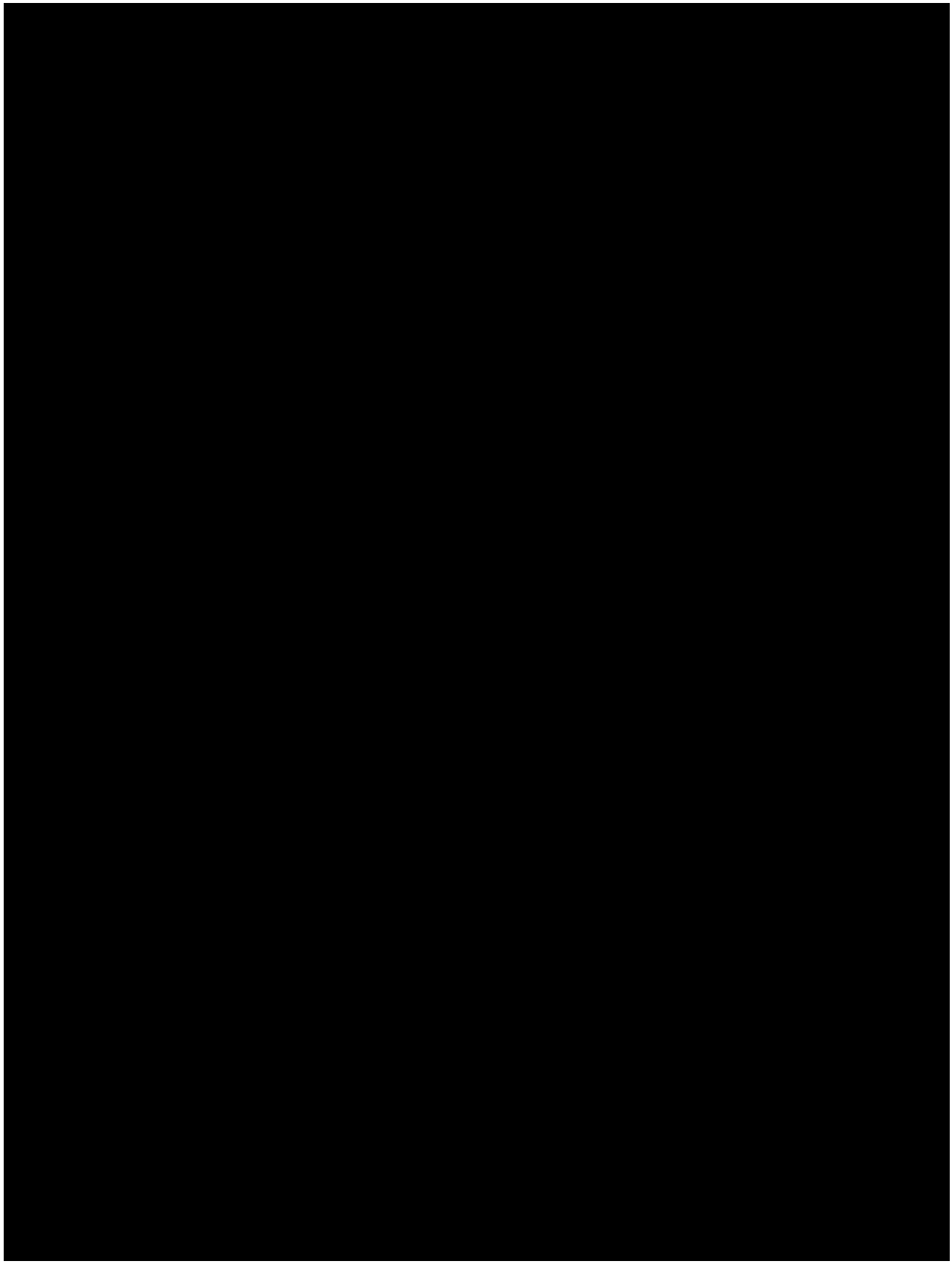
Part I: Nonmotor Aspects of Experiences of Daily Living	**Part II: Motor Experiences of Daily Living**
Cognitive impairment	Speech
Hallucinations and psychosis	Saliva and drooling
Depressed mood	Chewing and swallowing
Anxious mood	Eating tasks
Apathy	Dressing
Features of dopamine dysregulation syndrome	Hygiene
Sleep problems	Handwriting
Daytime sleepiness	Doing hobbies and other activities
Pain and other sensations	Turning in bed
Urinary problems	Tremor impact on activities
Constipation problems	Getting in and out of bed
Lightheadedness on standing	Walking and balance
Fatigue	Freezing
Part III: Motor Examination	**Part IV: Motor Complications**
Speech	Time spent with dyskinesias
Facial expression	Functional impact of dyskinesias
Rigidity (neck; right/left upper/lower extremities)	Painful *off* state dystonia
Finger tapping (right/left hands)	Time spent in the *off* state
Hand movements (right/left hands)	Functional impact of fluctuations
Pronation-supination movements of right/left hands	Complexity of motor functions
Toe tapping (right/left foot)	
Leg agility (right/left leg)	
Arising from chair	
Gait	
Freezing of gait	
Postural instability	
Posture	
Global spontaneity of movement (body bradykinesia)	
Postural tremor of right/left hands	
Kinetic tremor of right/left hands	
Rest tremor amplitude: right/left upper/lower extremities; lip jaw	
Constancy of rest tremor	

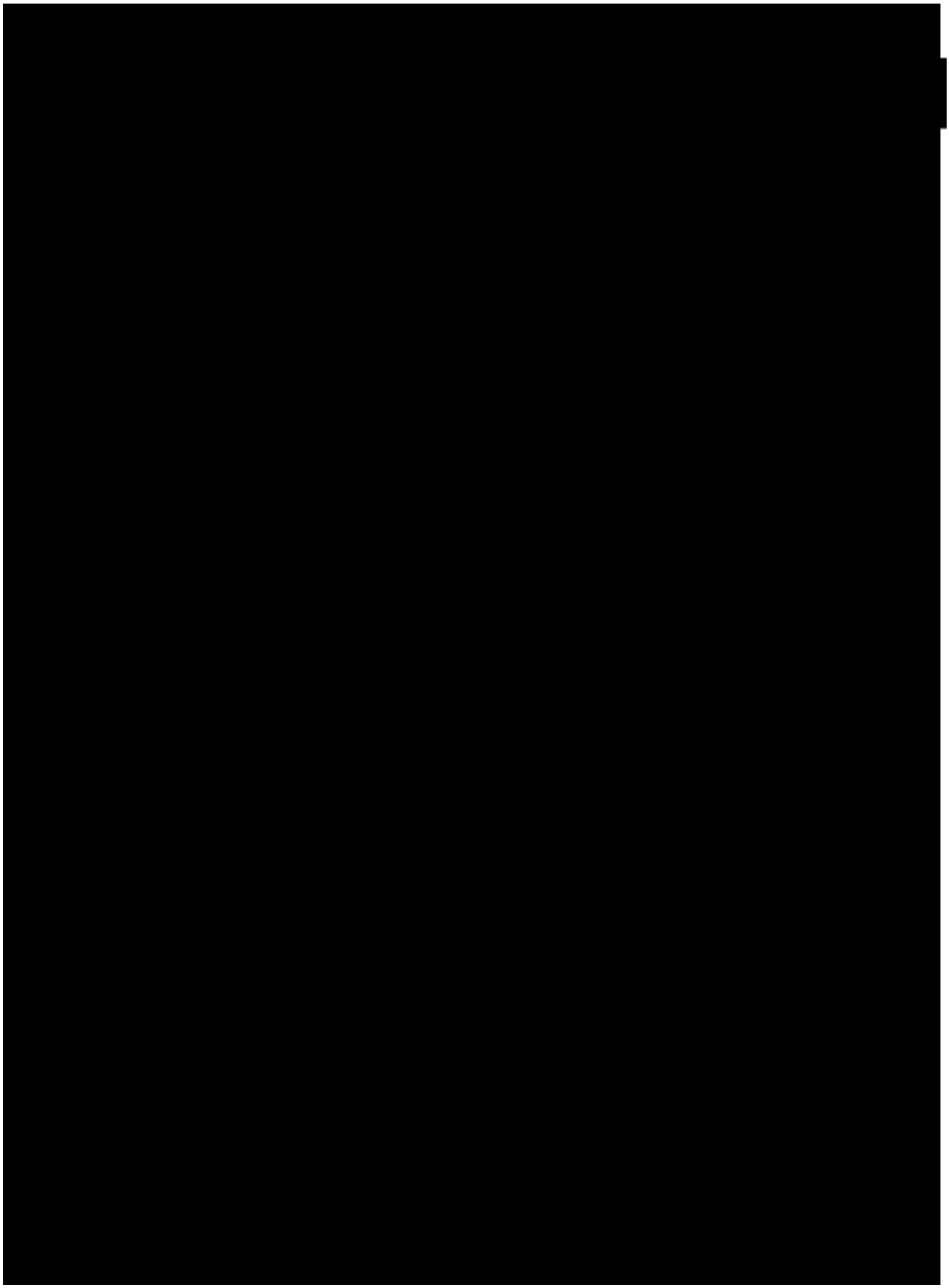


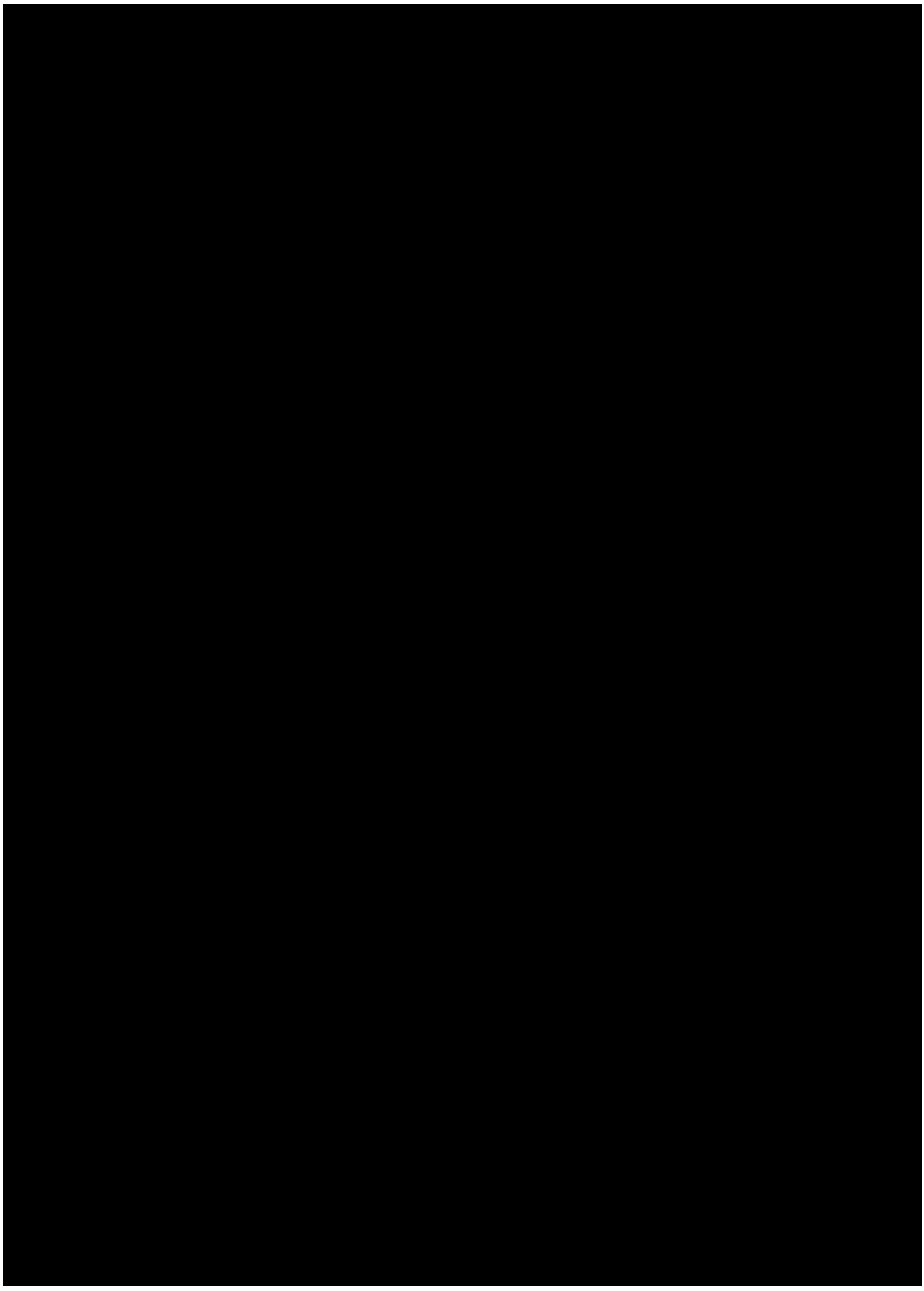


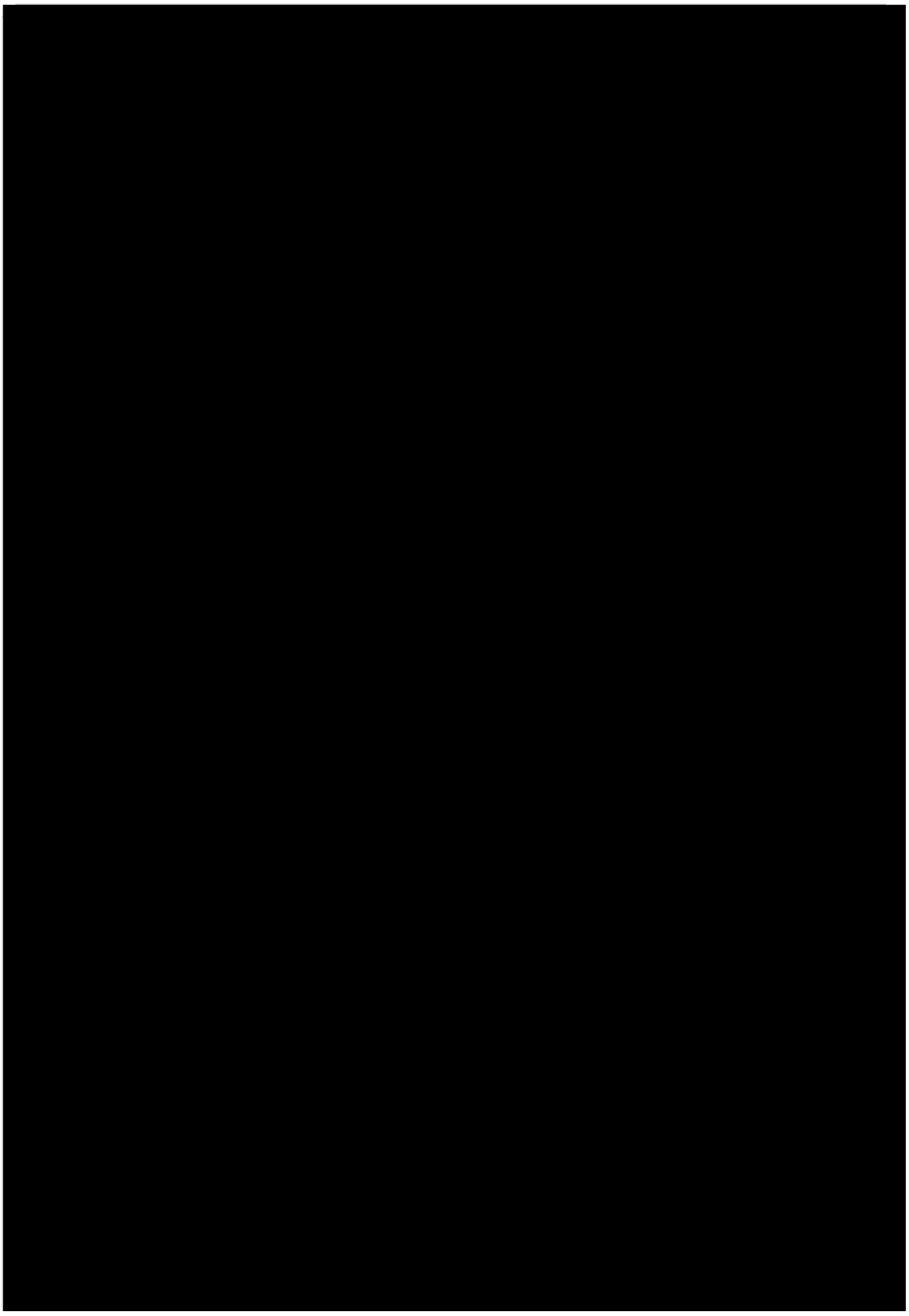












APPENDIX 10. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION AND SINCE LAST VISIT VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - *Most Severe Ideation:* ____ (*Type # (1-5)*) ____ (*Description of Ideation*) Past X Months - *Most Severe Ideation:* ____ (*Type # (1-5)*) ____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it....and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX 11. STANFORD SLEEPINESS SCALE (SSS)

This is a quick way to assess how alert you are feeling. If it is during the day when you go about your business, ideally you would want a rating of a one. Take into account that most people have two peak times of alertness daily, at about 9 a.m. and 9 p.m. Alertness wanes to its lowest point at around 3 p.m.; after that it begins to build again. Rate your alertness at different times during the day. If you go below a three when you should be feeling alert, this is an indication that you have a serious sleep debt and you need more sleep.

An Introspective Measure of Sleepiness
The Stanford Sleepiness Scale (SSS)

Degree of Sleepiness	**Scale Rating**
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

APPENDIX 12. MODIFIED OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (MOAA/S)

Modified Observer's Assessment of Alertness/Sedation Scale

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Summary of Changes to
Protocol 217-PRK-201, Amendment #4
Date of Amendment: 08 June 2017

The following changes were made in Protocol 217-PRK-201 v5.0, Amendment #4. In addition, minor editorial revisions (eg, formatting, punctuation) that are not listed below may have been made throughout the protocol.

Section Number and Title	**Original Text:**	**Changed To:**	**Rationale:**
Document Header	Amendment #3, Version 4.0	Amendment #~~3~~**4**, Version ~~4~~**5**.0	Administrative update
Title Page		**Date of Amendment 4 08 June 2017**	Administrative update
Protocol Signature Page	Date of Amendment 3: Version 4.0 06 June 2017	Date of Amendment 3: Version ~~4~~**5**.0 0~~6~~ **8** June 2017	Administrative update
2. Synopsis, Methodology	This study will assess the safety, tolerability, pharmacokinetics (PK) and effectiveness of SAGE-217. For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol. There are two parts, Part A and Part B, described below. Unique subjects will be enrolled in each part; subjects from Part A will not continue into Part B.	This study will assess the safety, tolerability, pharmacokinetics (PK) and effectiveness of SAGE-217. For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol. There are two parts, Part A and Part B, described below. ~~Unique subjects will be enrolled in each part; subjects from Part A will not continue into Part B.~~	Removed so subjects from Part A may be eligible for Part B.
2. Synopsis, Number of subjects (planned);	Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects	Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have	Changed to reflect that subjects from

Section Number and Title	**Original Text:**	**Changed To:**	**Rationale:**
7.2. Number of subjects	have completed Part A through Day 14 to inform the conduct of Part B. Up to 15 new 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).	completed Part A through Day 14 to inform the conduct of Part B. Up to 15 ~~new~~ 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).	Part A may be eligible for Part B.
2. Synopsis; 8.1. Subject Inclusion Criteria		**14. Part B only: Subjects who participated in Part A and meet all eligibility criteria for Part B must have tolerated at least 20 mg SAGE-217 in Part A, otherwise they are ineligible.**	Added criteria for Part B to exclude subjects that did not tolerate at least 20 mg dose in Part A
2. Synopsis, Duration of Treatment	Part A and Part B: Screening Duration: up to 28 days Treatment Period: 7 days Follow-up: 7 days Planned Study Duration per Subject: approximately 42 days	Part A and Part B: Screening Duration: up to 28 days **per part** Treatment Period: 7 days **per part** Follow-up: 7 days **per part** Planned Study Duration per Subject: approximately 42 days **if participating in one part only (up to 84 days if participating in both Parts A and B)**	Changes made for clarification for subjects that may participate in both parts of study
2. Synopsis, Statistical Methods, Sample Size Calculation	Approximately 18 subjects will be enrolled in Part A. Up to 15 new 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). The sample size for Part A and Part B was selected based on clinical and not statistical considerations.	Approximately 18 subjects will be enrolled in Part A. Up to 15 ~~new~~ 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). The sample size for Part A and Part B was selected based on clinical and not statistical considerations.	Changed to reflect that subjects from Part A may be eligible for Part B.

Section Number and Title	**Original Text:**	**Changed To:**	**Rationale:**
Table 3: Schedule of Events: Part B (Open-Label)		Added 'X' for Day 7 of MDS-UPDRS (Part II only) and MDS-UPDRS (Part III only)	Change made to show that MDS-UPDRS Part II/III only are to be performed 12 and 23 hours following the dose on Day 6 (ie, in the morning and evening of Day 7)
7.1 Overall Study Design	This study is a two-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 Oral Solution for 4 days in 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 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 not eligible to participate in Part B. Subjects will be followed for an additional 7 days after the administration of the last dose in Part A and Part B.	This study is a two-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 Oral Solution for 4 days in 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 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 ~~not~~ 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.	Changed to reflect that subjects from Part A may be eligible for Part B.
13.1.2. Vital Signs	Vital signs comprise respiratory rate, temperature, and supine (supine for at least 5 minutes prior to the	Vital signs comprise respiratory rate, temperature, and supine (supine for at least 5 minutes prior to the	Change made to distinguish between

Section Number and Title	Original Text:	Changed To:	Rationale:
	measurement) and standing systolic and diastolic blood pressure and heart rate. Vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in AM of Day 8; and on Day 14. Vital signs and pulse oximetry are to be assessed within ±10 minutes of the scheduled times through the 4 hour time point and within ±15 minutes of the scheduled times for the 6-hour through 16-hour time points. In Part B, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, and 12 hours postdose on Days 1 through 7; and on Day 14. Vital signs and pulse oximetry are to be assessed within ±10 minutes of the 1- and 2 hour time points and within ±15 minutes of the 12-hour time point.	measurement) and standing systolic and diastolic blood pressure and heart rate. **In Part A, v**~~V~~ital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in AM of Day 8; and on Day 14. Vital signs and pulse oximetry are to be assessed within ±10 minutes of the scheduled times through the 4 hour time point and within ±15 minutes of the scheduled times for the 6-hour through 16-hour time points. In Part B, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, and 12 hours postdose on Days 1 through 7; and on Day 14. Vital signs and pulse oximetry are to be assessed within ±10 minutes of the 1- and 2 hour time points and within ±15 minutes of the 12-hour time point.	Part A and Part B assessments
13.2.1.4. Recording Sedation as an Adverse Event	In Part A and Part B, sedation will be assessed using protocol-specified rating scales. Consideration should be given to the most appropriate term to describe the sedation characteristics. For Part A, in order to standardize the reporting of sedation as adverse events, Investigators must record sedation as an adverse event if there is a score of >5 on the SSS and/or a score of ≤2 on the MOAA/S. SSS and MOAA/S do not apply to Part B.	In Part A and Part B, sedation will be ~~assessed using protocol-specified rating scales~~**recorded as an adverse event**. Consideration should be given to the most appropriate term to describe the sedation characteristics. For Part A, in order to standardize the reporting of sedation as adverse events, Investigators must record sedation as an adverse event if there is a score of >5	Clarification

Section Number and Title	Original Text:	Changed To:	Rationale:
		on the SSS and/or a score of ≤2 on the MOAA/S. SSS and MOAA/S do not apply to Part B.	
14.8. Determination of Sample Size	Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14. Up to 15 new 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). 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 in subjects with PD.	Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14. Up to 15 ~~new~~ 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). 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 in subjects with PD.	Changed to reflect that subjects from Part A may be eligible for Part B.

PROTOCOL NUMBER: 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

IND NUMBER: 131,258

Investigational Product	SAGE-217
Clinical Phase	2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted], M.D., Ph.D. [redacted] Phone: [redacted] Email: [redacted]
Sponsor Medical Monitor	[redacted], M.D., M.P.H. Study Physician Phone: [redacted] Email: [redacted]
Date of Original Protocol	28 September 2016
Date of Amendment 1	5 October 2016
Date of Amendment 2	24 October 2016
Date of Amendment 3	06 June 2017

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

PROTOCOL SIGNATURE PAGE

Protocol Num ber:	217 -PRK-201
Product:	SAGE-217
IND No.:	131,258
Study Phase:	2
Sponsor:	Sage Therapeutics
Date of Amendment 3:	Version 4.0 06 June 2017

Sponsor Approval

[redacted] 06 Jun 2017

[redacted] M.D., Ph.D. Date (DD/MMM/YYYY)

[redacted]
Sage Therapeutics

[redacted] 6 June 2017

[redacted] Pharm.D, M.S., R.Ph. Date (DD/MMM/YYYY)

[redacted] 06 JUN 2017

[redacted] M.S.H.S. Date (DD/MMM/YYYY)

[redacted]
Sage Therapeutics

[redacted] 06 Jun 2017

[redacted] MS Date (DD/MMMNYYY)

[redacted]
Sage Therapeutics

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the Clinical Protocol 217-PRK-201 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

CONTACTS IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Research Organization	[redacted]	[redacted]

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics
215 First Street
Cambridge, MA 02142

Name of Investigational Product:
SAGE-217 Oral Solution
SAGE-217 Capsules

Name of Active Ingredient:
SAGE-217

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

Study centers: Up to 12 centers

Objectives

Primary:

Part A:

- To evaluate the safety and tolerability of SAGE-217 Oral Solution.

Part B:

- To evaluate the effect of SAGE-217 Capsules as an adjunct to antiparkinsonian agent(s) on the severity of PD tremor symptoms.

Secondary:

Part A:

- 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.

Part B:

- 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.

Pharmacokinetic:

- **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.

Endpoints

Primary:

Part A:

- Frequency and severity of adverse events and changes 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 (SSS) score.

Part B:

- Improvement in PD tremor as assessed by changes in the MDS UPDRS Part VIII tremor score (defined as the sum of MDS-UPDRS items 2.10, 3.15, 3.16, 3.17 and 3.18).

Secondary:

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) score.

Part B:

- 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.
- Frequency and severity of adverse events and changes in vital signs, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS).

Pharmacokinetic:

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

Exploratory:

[redacted]

[redacted]

Methodology:

This study will assess the safety, tolerability, pharmacokinetics (PK) and effectiveness of SAGE-217. For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol.

There are two parts, Part A and Part B, described below. Unique subjects will be enrolled in each part; subjects from Part A will *not* continue into Part B.

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

All subjects will continue to take their antiparkinsonian agent(s) including immediate-release oral Levodopa on the day of admission (Day -1) and in the AM only 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. Subjects not tolerating 30 mg will receive 20 mg, and subjects not tolerating 20 mg will receive 10 mg on subsequent days. 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 in order to inform the conduct of Part B.

Assessments will be performed periodically during the study as outlined in the Schedule of Events for Part A (Table 2).

Part B: Open-label with evening (PM) dosing, for 7 days, as an adjunct to antiparkinsonian agent(s).

Subjects on a stable dose of antiparkinsonain 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 adverse event 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 adverse event 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. 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 B (Table 3).

Number of subjects (planned):

Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14 to inform the conduct of Part B.

Up to 15 new 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).

Inclusion Criteria:

1. Subject has signed an informed consent form (ICF) before any study-specific procedures are performed.
2. Subject is between 40 and 75 years of age, inclusive.
3. Subject has a diagnosis of idiopathic PD based on modified UK Brain Bank Criteria (modified to allow individuals with a family history of PD) (Hughes 1992; Appendix 1).
4. **Part A**: Subjects with PD with a duration of less than 7 years and must meet the criteria for Hoehn and Yahr stage 2 or stage 3 (Appendix 2).
   Part B: Subjects with PD and must meet the criteria for Hoehn and Yahr stage 1-4 (Appendix 2) assessed during the "on" period (assumed to be within 2 hours of dosing with antiparkinsonian agent(s)), and have a tremor with a MDS-UPDRS Part II/III tremor score of ≥8 (sum of items: 2.10, 3.15, 3.16, 3.17 and 3.18) AND a MDS-UPDRS item score ≥3 in at least one limb (from items 3.15, 3.16, or 3.17). Inclusion criteria tremor scores must be assessed during "on" periods during the screening and Day -1 visit.
5. **Part A**: Subject has a stable dose of antiparkinsonian agent(s) including immediate-release oral Levodopa or Carbidopa-Levodopa (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.
   Part B: Subject is receiving a stable dose of antiparkinsonian agent(s) (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.
6. **Part A only**: Subject is willing to discontinue his/her treatment with immediate-release oral Levodopa or Carbidopa-Levodopa for at least 8 hours prior to dosing with SAGE-217.
7. **Part A**: Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) or amantadine at least 5 days prior to the day of admission (Day -1).
   Part B: Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) by Day -6 or amantadine by Day -10.
8. Subjects taking an antidepressant drug, sleep medication, or neuroleptic must have been on a stable dose for at least 1 month prior to the baseline visit.
9. Subjects must have a MoCA score of >22.
10. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests.
11. **Part A**: Female subjects must agree to practice a highly effective method of birth control while on study through completion of the last follow-up visit. If a subject discontinues early after receiving

a dose of SAGE-217, then the subject must continue this method of birth control for at least 7 days following the last dose of study drug. Highly effective methods of birth control include combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence.
Part B: Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause) and/or surgically sterile:

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception
- associated with inhibition of ovulation.
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner.
- Sexual abstinence (no sexual intercourse).

12. Male subjects must agree to practice a highly effective method of birth control while on study, and for 13 weeks after receiving the last dose of study drug. Effective methods of birth control include sexual abstinence, vasectomy, or a condom with spermicide (men) in combination with their partner's highly effective method.
13. Males must be willing to abstain from sperm donation and females from donating eggs while on study through 13 weeks after receiving the last dose of study drug.

Exclusion Criteria:

1. Subjects with a known hypersensitivity to SAGE-217 Oral Solution or its major excipient, HPβCD (**Part A**) or SAGE-217 Capsule or its excipients (**Part B**).
2. **Part A**: Subjects with early PD (Hoehn and Yahr stage 1) or advanced PD (Hoehn and Yahr stage 4 or stage 5).
   Part B: Subjects with advanced PD (Hoehn and Yahr stage 5).
3. Subjects with any medical or psychiatric condition that jeopardizes/compromises his/her ability for participation. This includes schizophrenia spectrum and other psychotic disorders, substance-related and addictive disorders, feeding and eating disorders, bipolar and related disorders, structural brain disease including but not limited to history of encephalitis or hydrocephalus and history of clinically significant stroke, or anticipating starting psychotherapy or behavior therapy during the course of the study or who started psychotherapy or behavior therapy within 30 days prior to Day 1.
4. Subjects with a history of:
   a. Electroconvulsive therapy;
   b. Stereotaxic brain surgery (deep brain stimulation) for PD;

c. History of suicide attempt within 2 years, or has answered YES to questions 3, 4, or 5 on the C SSRS at the screening or Day -1 visits, or has current suicidal ideation; or

d. Impulse control disorder.

5. **Part A**: Subjects with severe depression as defined by a BDI-II score >19.
6. **Part B**: Subject has recent exposure (14 days prior to the Day -1 visit) to tremorogenic drugs, as defined in Appendix 4.
7. Subjects with Type I or Type II diabetes mellitus.
8. Subjects with presence of drug-induced parkinsonism (eg, metoclopramide, flunarizine), metabolic identified neurogenetic disorders (eg, Wilson's disease), encephalitis, or other atypical Parkinsonian syndromes (eg, progressive supranuclear palsy, multiple system atrophy).
9. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.
10. Subject has clinically significant abnormal physical examination OR 12-lead ECG at the screening or admission visits. NOTE: QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study. ECG may be repeated once if initial values obtained are outside the specified limits.
11. Subject has a history, presence and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies 1 and 2.
12. Subject has exposure to another investigational medication or device within 30 days prior to Day 1.
13. Subject has donated one or more units of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing (1 unit = 450 mL).
14. Subject is unwilling or unable to comply with study procedures.
15. Subjects has used any known strong inhibitors and/or inducers of cytochrome P450 (CYP)3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.

Investigational product, dosage and mode of administration:

Part A: SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dose.

Part B: SAGE-217 Capsules are available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients. For Part B, capsules will be available in 5-mg, 10-mg and 20-mg dose strengths. Subjects will be administered two capsules per dose.

Duration of treatment:

Part A and Part B:

Screening Duration: up to 28 days
Treatment Period: 7 days
Follow-up: 7 days
Planned Study Duration per Subject: approximately 42 days

Reference therapy, dosage, and mode of administration:

Not applicable; Part A and Part B are open-label with all subjects receiving SAGE-217.

Criteria for evaluation:

Safety and tolerability:

Safety and tolerability of study drug will be evaluated by vital signs, clinical laboratory measures, ECGs, physical examinations, concomitant medication usage, C-SSRS, and adverse event reporting. Sleepiness/sedation will be assessed by the SSS in Part A only.

Efficacy:

Part A:

- Improvement in PD motor symptoms and overall symptoms will be assessed by changes in the MDS UPDRS Part III score and MDS-UPDRS Parts I-IV total score at various time points.

Part B:

- Improvement in PD tremor as assessed by changes in the 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).
- 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.

Pharmacokinetics:

Plasma will be collected to assay for concentrations of SAGE-217 and possibly SAGE-217 metabolites in Part A and Part B.

Part A: The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), the distributional half-life and terminal half-life ($t_{1/2}$), and steady-state drug concentration in the plasma (C_{ss}).

Part B: Area under the curve (AUC), C_{max}, and trough concentration (C_{0h}) at steady-state will be estimated for each individual using the most recent applicable Population PK model.

Statistical Methods:

Sample Size Calculation

Approximately 18 subjects will be enrolled in Part A. Up to 15 new 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). The sample size for Part A and Part B was selected based on clinical and not statistical considerations.

Study Populations

The safety population, defined as all subjects who are administered at least one dose of study drug, will be used to provide descriptive summaries of safety.

The efficacy population, defined as all subjects in the safety population who receive at least one dose of study drug and have at least one postdose MDS-UPDRS evaluation, will be used to analyze efficacy data.

The PK population will consist of all subjects in the safety population with at least one plasma sample with sufficient plasma concentrations for PK evaluations and will be used to summarize PK data.

Separate populations will be defined for each part of the study.

General Considerations

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

Safety Analysis

Adverse events will be coded using Medical Dictionary for Regulatory Activities™ (MedDRA). The overall incidence of adverse events will be displayed by System Organ Class (SOC), preferred term, dose group, and cohort. Incidence of adverse events will also be presented by maximum severity and relationship to study drug. Vital signs, clinical laboratory measures, ECG, and C-SSRS data will be summarized by dose group and total, where applicable. Out-of-range safety endpoints may be categorized as low or high, where applicable. Subject listings will be provided for all safety data.

Efficacy Analysis

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data.

An interim analysis of 10 subjects completing Part A is planned to inform Part B study conduct. No formal interim analysis for Part B subjects is planned.

Pharmacokinetic Analysis

Drug concentrations and pharmacokinetic parameters will be summarized using appropriate descriptive statistics and listed by subject.

Table 2: Schedule of Events: Part A (Open-Label)

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]											

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)
[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 Admission (Day -1); predose for Day 4, Day 6, and Day 8; and Day 14

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

[d] Vital Signs: Screening and 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. 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 be used 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 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 Part III only should also take place on Admission (Day -1).

[redacted]

[p] Plasma PK sampling times (±5 minutes): Day 4 predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose; predose 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

Table 3: Schedule of Events: Part B (Open-Label)

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[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	X									
CBC/Serum Chemistry[b]	X	X[c]				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)
Plasma PK Samples[r]			X	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X
Administer SAGE-217[s]			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]; [redacted]; [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 da ys); at 8AM (±1 hour) on Day l; 12 (±15 1ninutes) 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 antiparkinsonianagent(s).

k MDS-UPDRS (Part II/III only): 12 and 23 **(±15**1ninutes) hours postdose on Confinement Days 1, 2, 3, 4, *5* , and 6. MDS-UPDRS Part 11/111s hould take place during the "on" period AND within 2 hours of dosing with antiparkinsonian agent(s).

I [redacted]

r Plasma PK sampling times (±1 hour): predose and 13 hours postdose on Day l; and 13 hours postdose on Days 2 through 7.

[5] SAGE-217 Capsules are to be adrninistered in the evening (8PM ±30 minutes) with food.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

1. TITLE PAGE 1
2. SYNOPSIS 5
3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 19
4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 24
5. INTRODUCTION 26
5.1. Background of Parkinson's Disease and Unmet Medical Need 26
5.2. SAGE-217 27
5.3. Summary of Nonclinical and Clinical Experience with SAGE-217 27
5.3.1. Nonclinical Studies with SAGE-217 27
5.3.2. Clinical Experience 27
5.4. Potential Risks and Benefits 29
6. TRIAL OBJECTIVES AND PURPOSE 31
6.1. Primary Objective 31
6.2. Secondary Objectives 31
6.3. Pharmacokinetic Objectives 31
6.4. Endpoints 31
6.4.1. Primary Endpoints 31
6.4.2. Secondary Endpoints 32
6.4.3. Pharmacokinetic Endpoints 32
6.4.4. Exploratory Endpoints 32
7. INVESTIGATIONAL PLAN 34
7.1. Overall Study Design 34
7.2. Number of Subjects 35
7.3. Treatment Assignment 35
7.4. Dose Adjustment Criteria 35
7.5. Criteria for Study Termination 36
8. SELECTION AND WITHDRAWAL OF SUBJECTS 38
8.1. Subject Inclusion Criteria 38
8.2. Subject Exclusion Criteria 39

8.3. Subject Withdrawal Criteria 41
9. TREATMENT OF SUBJECTS 42
9.1. Description of Study Drug Treatment 42
9.1.1. Part A 42
9.1.2. Part B 42
9.2. Concomitant Medications 42
9.2.1. Prior/Concomitant Medications 42
9.2.2. Prohibited Medications 43
9.3. Treatment Compliance 43
9.4. Randomization and Blinding 43
10. STUDY DRUG MATERIALS AND MANAGEMENT 44
10.1. Study Drug 44
10.1.1. SAGE-217 Oral Solution 44
10.1.2. SAGE-217 Capsule 44
10.2. Study Drug Packaging and Labeling 44
10.3. Study Drug Storage 44
10.4. Study Drug Preparation 45
10.5. Administration 46
10.6. Study Drug Accountability 46
10.7. Study Drug Handling and Disposal 46
11. ASSESSMENT OF EFFICACY 47
11.1. Movement Disorder Society – Unified Parkinson's Disease Rating Scale 47
11.2. Exploratory Endpoints 48
[redacted] [redacted] 48
[redacted] [redacted] 49
[redacted] [redacted] 49
[redacted] [redacted] 49
[redacted] [redacted] 50
[redacted] 50
12. PHARMACOKINETICS 52
12.1. Blood Sample Collection 52
12.2. Storage and Shipment of Pharmacokinetic Samples 52

12.3. Sample Analysis 52
13. ASSESSMENT OF SAFETY 53
13.1. Safety and Tolerability Parameters 53
13.1.1. Demographic/Medical History 53
13.1.2. Vital Signs 53
13.1.3. Weight and Height 53
13.1.4. Physical Examination 53
13.1.5. Electrocardiogram (ECG) 53
13.1.6. Laboratory Assessments 54
13.1.6.1. Hematology 54
13.1.6.2. Blood Chemistry 54
13.1.6.3. Urinalysis 54
13.1.6.4. Virus Serology 54
13.1.6.5. Pregnancy Screen 55
13.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS) 55
13.1.8. Stanford Sleepiness Scale (SSS) 55
13.1.9. Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) 55
13.2. Adverse and Serious Adverse Events 56
13.2.1. Definition of Adverse Events 56
13.2.1.1. Adverse Event 56
13.2.1.2. Suspected Adverse Reaction 56
13.2.1.3. Serious Adverse Event 56
13.2.1.4. Recording Sedation as an Adverse Event 57
13.2.2. Pregnancy 57
13.3. Relationship to Study Drug 57
13.4. Recording Adverse Events 58
13.5. Reporting Serious Adverse Events 58
14. STATISTICAL METHODS AND CONSIDERATIONS 60
14.1. Data Analysis Sets 60
14.2. Handling of Missing Data 60
14.3. General Considerations 60
14.4. Demographics and Baseline Characteristics 60

14.5. Efficacy Endpoints....60
14.5.1. Secondary Efficacy Endpoints....61
14.5.2. Exploratory Efficacy Endpoints....61
14.6. Safety and Tolerability Analyses....61
14.6.1. Adverse Events....61
14.6.2. Vital Signs....61
14.6.3. Physical Examinations....62
14.6.4. 12-Lead ECG....62
14.6.5. Clinical Laboratory Evaluations....62
14.6.6. Columbia-Suicide Severity Rating Scale (C-SSRS)....62
14.6.7. Stanford Sleepiness Scale (SSS)....62
14.6.8. Modified Observer's Assessment of Alertness/Sedation (MOAA/S)....62
14.6.9. Prior and Concomitant Medications....62
14.7. Pharmacokinetic Analysis....63
14.8. Determination of Sample Size....63
14.9. Changes From Protocol Specified Analyses....63
15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS....64
15.1. Study Monitoring....64
15.2. Audits and Inspections....64
15.3. Institutional Review Board (IRB)....65
16. QUALITY CONTROL AND QUALITY ASSURANCE....66
17. ETHICS....67
17.1. Ethics Review....67
17.2. Ethical Conduct of the Study....67
17.3. Written Informed Consent....67
18. DATA HANDLING AND RECORDKEEPING....68
18.1. Inspection of Records....68
18.2. Retention of Records....68
18.3. Confidentiality....68
19. PUBLICATION POLICY....70
20. LIST OF REFERENCES....71
21. APPENDICES....73

APPENDIX 1. UNITED KINGDOM BRAIN BANK CRITERIA 74
APPENDIX 2. HOEHN AND YAHR STAGING CRITERIA 75
APPENDIX 3. ANTICHOLINERGIC DRUGS 76
APPENDIX 4. TREMOROGENIC DRUGS 77
APPENDIX 5. MOVEMENT DISORDER SOCIETY-UNIFIED PARKINSON'S DISEASE RATING SCALE (MDS-UPDRS) 79
[redacted] 80
[redacted] 83
[redacted] 86
[redacted] 87
APPENDIX 10. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION AND SINCE LAST VISIT VERSION 90
APPENDIX 11. STANFORD SLEEPINESS SCALE (SSS) 96
APPENDIX 12. MODIFIED OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (MOAA/S) 97

LIST OF TABLES

Table 1: Emergency Contact Information 4
Table 2: Schedule of Events: Part A (Open-Label) 13
Table 3: Schedule of Events: Part B (Open-Label) 16
Table 4: Abbreviations and Specialist Terms 24
Table 5: Batch Formula for 125 mL of Stock SAGE-217 Oral Solution 6 mg/mL 45
Table 6: Rating Scale for the MDS-UPDRS 47

LIST OF FIGURES

Figure 1: Study Design of Part A 37
Figure 2: Study Design of Part B 37

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ALT	alanine aminotransferase
AM	morning
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
[redacted]	[redacted]
BMI	body mass index
CBC	complete blood count
C_{max}	maximum plasma concentration
CRF	case report form
CS	clinically significant
Css	steady-state drug concentration in the plasma
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic CRF
EP	European Pharmacopeia
GABA	γ aminobutyric acid
$GABA_A$	γ aminobutyric acid-ligand gated chloride channel
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPβCD	hydroxypropyl-β-cyclodextrin
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
Levodopa/Carbidopa	Levodopa or Carbidopa-Levodopa
MDS	Movement Disorder Society
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
MoCA	Montreal Cognitive Assessment
MTD	maximum tolerated dose
n	number
NCS	not clinically significant
NF	National Formulary
PD	Parkinson's disease
[redacted]	[redacted]
PK	pharmacokinetic(s)
PM	evening
QTcF	QT interval calculated using the Fridericia method
SOC	system organ class
SRC	Safety Review Committee
SSS	Stanford Sleepiness Scale
TEAE	treatment-emergent adverse event
$t_{1/2}$	terminal half-life
t_{max}	time to reach maximum concentration
USP	United States Pharmacopeia
WHO	World Health Organization

5. INTRODUCTION

5.1. Background of Parkinson's Disease and Unmet Medical Need

Parkinson's disease (PD) is a chronic progressive neurodegenerative condition that affects the motor, autonomic, cognitive, and sensory systems. Parkinson's disease is the second most common neurodegenerative disorder (Bergman 2002) and is associated with a massive loss of dopaminergic cells in the substantia nigra, leading to dopamine hypofunction and alteration of the basal ganglia circuitry. Dopamine neurons are under the control of the excitatory glutamatergic and inhibitory γ-aminobutyric acid (GABA) systems. Imbalance between the glutamatergic and GABA systems may contribute to excitotoxicity and dopaminergic cell death.

The motor symptoms of PD have been linked with a loss of dopamine neurons in the substantia nigra pars compacta and a consequential reduction in the level of dopamine input in the striatum (Siderowf 2012). These symptoms evolve slowly and are characterized by the progression of tremor, rigidity, bradykinesia, and postural instability. Tremor caused by PD can appear as either a resting tremor or an action tremor. The most typical tremor of PD is a "pill-rolling" rest tremor between the thumb and index finger. Not everyone with PD develops a tremor, and those who do experience tremor may have symptoms that come and go. Typically, PD tremor starts in the fingers of one hand before spreading to affect the rest of the arm. Tremor can also spread to affect the foot on the same side of the body and, after several years, the tremor can spread to affect the other side of the body. Without treatment, PD tremor usually worsens over time.

At present, there is no cure for PD. The core symptoms are caused by the degeneration of dopamine-producing neurons and, therefore, treatment consists of dopamine replacement. While enormous progress has been made in the treatment of PD over the past half century, levodopa remains the most potent drug for controlling PD symptoms (Jankovic 2008). The addition of carbidopa, a peripheral dopa decarboxylase inhibitor, enhances the therapeutic benefits of levodopa. However, levodopa therapy is frequently associated with motor complications, and the appropriate time to initiate levodopa therapy continues to be debated (Stern 2004; Weiner 2004). The majority of patients treated with levodopa experience motor fluctuation, dyskinesia or other complications after 5 years of treatment (Jankovic 2005).

Neurosteroids, a group of steroid hormones synthesized in the brain, modulate the function of several neurotransmitter systems. The substantia nigra expresses high concentrations of allopregnanolone, a neurosteroid that positively modulates the action of GABA at γ-aminobutyric acid-ligand gated chloride channel ($GABA_A$) receptors. In PD patients, decreased plasma and cerebrospinal fluid levels of the neurosteroid allopregnanolone and 5α-dihydroprogesterone have been observed (di Michele 2003).

Parkinson's disease is the second most common chronic neurodegenerative disease, affecting about 1 million people in the United States and more than 4 million people worldwide. It has a devastating effect on patients and is often accompanied by tremendous physical and emotional burden not only for the patients but also for their families and friends. As the size of the elderly population grows, the burden of PD is projected to grow substantially over the next few decades. To date, the therapy of PD is symptomatic, aimed at ameliorating motor symptoms. Although the goal of therapy is to reverse the functional disability, abolition of all symptoms and signs is not currently possible, even with high doses of medication. Thus, there is a growing need for

innovative new treatments to prevent, delay onset, or alleviate symptoms of PD. Neurosteroids act as neuroprotectants and as $GABA_A$-receptor agonists in the physiology and pathology of the basal ganglia, impact dopaminergic cell activity and survival, and may therefore represent potential therapeutics in PD.

5.2. SAGE-217

SAGE-217 is a positive allosteric modulator of the $GABA_A$ receptor and thus is expected to be of benefit for the treatment of PD.

Two dosage forms of SAGE-217 for oral administration will be used in this study (SAGE-217 Oral Solution in Part A and SAGE-217 Capsules in Part B).

SAGE-217 Oral Solution 6 mg/mL (40% w/w aqueous hydroxypropyl-β-cyclodextrin [HPβCD] with 0.025 mg/mL sucralose) is a non-viscous, clear solution.

SAGE-217 Capsules are available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the active, SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients.

5.3. Summary of Nonclinical and Clinical Experience with SAGE-217

5.3.1. Nonclinical Studies with SAGE-217

In nonclinical studies of SAGE-217, sedative-hypnotic effects were consistently observed at higher doses in both in vivo pharmacology studies and in toxicology studies. The sedative-hypnotic impairments seen with SAGE-217 were typical for $GABA_A$-positive modulators, ranging from hyperexcitability and ataxia at the lower doses through deep sedation and ultimately anesthesia at higher doses. Depth and duration of sedation demonstrated a clear dose response over the range tested, with evidence of tolerance occurring with continued exposure. Tolerance to the effects of SAGE-217 on motor incoordination was not observed after 7 days of dosing.

The compound has been assessed in 14-day rat and dog toxicology studies with daily administration of SAGE-217 as a solution in HPβCD in dogs and Labrasol® in rats. The no observed adverse effect level was 3 mg/kg (females) and 22.5 mg/kg (males) in rats and 2.5 mg/kg in dogs. There were no adverse effects in dogs or rats in the main toxicology studies. A single observation of mortality occurred in one female rat at the high dose in a toxicokinetic study that was suspected to have been related to exaggerated pharmacology. Additional toxicology and pharmacology information is provided in the Investigator's Brochure.

5.3.2. Clinical Experience

To date, two clinical studies employing SAGE-217 Oral Solution are clinically complete and final clinical study reports are pending. Discussions of pharmacokinetic (PK) data are limited to the single-ascending dose, food effect, and essential tremor cohorts from Study 217-CLP-101 and the multiple-ascending dose and drug-drug interaction cohorts from Study 217-CLP-102. Discussions of safety data are limited to the single-ascending dose cohorts in Study 217-CLP-101 and the multiple-ascending dose cohorts in Study 217-CLP-102. In addition, one

clinical study of the safety, tolerability, PK, and relative bioavailability SAGE-217 Capsules is clinically complete and the final study report is pending. The results of this study (217-CLP-103) are briefly described below.

Study 217-CLP-101 was a first-in-human, four-part study that assessed the effects of a single dose of SAGE-217 Oral Solution. The study was a double-blind, placebo-controlled, single-ascending dose design in healthy adult volunteers, with the objective of identifying the maximum tolerated dose (MTD) and PK profiles of SAGE-217 Oral Solution. Subjects in each of the single-ascending dose cohorts received a single dose of study drug, either SAGE-217 Oral Solution (six subjects) or placebo (two subjects), with SAGE-217 Oral Solution doses of 0.25 mg, 0.75 mg, 2 mg, 5.5 mg, 11 mg, 22 mg, 44 mg, 55 mg, and 66 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the Safety Review Committee (SRC) and agreement reached that it was safe to increase the dose. The MTD was determined to be 55 mg. Two cohorts, 6 subjects each, received SAGE-217 Oral Solution in an open-label manner (one cohort received 50% of the MTD [22 mg] to study the food effects and the other cohort received the MTD [55 mg] to study the effects on subjects with essential tremor). SAGE-217 Oral Solution was orally bioavailable, demonstrated dose-linear PK from the lowest (0.25 mg) through the highest (66 mg) dose, and supported once-daily oral dosing with food. In addition, the pharmacodynamic effects of the SAGE-217 Oral Solution MTD were assessed in placebo-controlled, blinded, crossover electroencephalogram cohorts of 8 subjects each; one cohort received 50% of the MTD (22 mg) and the other received the MTD (55 mg).

Study 217-CLP-102 was a two-part study that assessed the effects of multiple-ascending doses of SAGE-217 Oral Solution. The study was a double-blind, placebo-controlled, multiple-ascending dose study in healthy adult volunteers. Subjects in each of the multiple-ascending dose cohorts received study drug, either SAGE-217 Oral Solution (nine subjects) or placebo (three subjects), once daily for 7 days, with SAGE-217 Oral Solution doses of 15 mg, 30 mg, and 35 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the SRC and agreement reached that it was safe to increase the dose. The MTD was determined to be 30 mg. It was observed that subjects receiving the drug in the evening did better in terms of tolerability compared to when they received the drug in the morning. A fourth cohort of 12 subjects received 30 mg of SAGE-217 Oral Solution in an open-label manner to study drug-drug interactions. SAGE-217 Oral Solution is not likely to induce the metabolism of cytochrome P450 (CYP)2B6 or CYP3A4 substrates. SAGE-217 Oral Solution was orally bioavailable and suitable for once-daily oral dosing at night time with food.

SAGE-217 Oral Solution was generally well tolerated. In both Phase 1 studies (217-CLP-101 and 217-CLP-102), doses were escalated until the stopping criteria were met. Most adverse events were reported as mild or moderate in intensity, and there were no serious adverse events reported in either study. In addition, none of the observed adverse events resulted in discontinuation of the study drug. At doses planned for further study, the observed sedation was mild, transient, and associated with daily peak exposure. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, dizziness, euphoric mood, fatigue, tremor, and muscle twitching, reported most frequently in the highest dose group (66 mg). Some changes in mean blood pressure and heart rate were observed after single doses of 44 mg and greater. After multiple doses of 30 mg (morning [AM] or evening [PM]) or 35 mg (AM) over 7 days, there was no evidence of changes in mean vital sign measures even though Day 7 plasma

concentrations approximated that of the highest single dose in the single-ascending dose study. Subjects seemed to tolerate SAGE-217 Oral Solution better when given as night time dosing.

The safety, tolerability, PK, and relative bioavailability of the SAGE-217 Capsules were assessed in a Phase 1 randomized, open-label, cross-over study (Study 217-CLP-103). In the fasted state, SAGE-217 Capsules demonstrated reduced exposure in terms of maximum (peak) plasma concentration (C_{max}) and area under the curve from zero to the time of the last quantifiable concentration (AUC_{last}) compared to SAGE-217 Oral Solution. SAGE-217 Capsules administered in the fed state (with standard and high-fat meal) showed increased exposure compared to the fasted state and approximately equivalent exposure in terms of geometric mean AUC_{last} compared to SAGE-217 Oral Solution; however, the C_{max} for SAGE-217 Capsules was reduced by approximately 50% when compared with SAGE-217 Oral Solution. Based on these study results, exposures with SAGE-217 Capsules are anticipated to be equal to or less than exposures observed at the same dose with SAGE-217 Oral Solution.

Neuroactive steroids are a class of endogenous and synthetic positive allosteric modulators that target both synaptic and extra-synaptic $GABA_A$ receptors (Belelli 2002 and confirmed in the Sponsor's in vitro studies). This diverse activity profile suggests that neuroactive steroid $GABA_A$ receptor-positive allosteric modulators could exhibit robust activity against essential tremor. Administration of SAGE-547 injection, a proprietary formulation of the endogenous neuroactive steroid, resulted in significant reductions in upper limb kinetic tremor scores compared to placebo in a Phase 2 proof-of-principle study (IND 122,280). Based on these results with SAGE-547, the study design for single-ascending dose study 217-CLP-101 included a cohort of subjects with essential tremor (N=6) who received SAGE-217 Oral Solution (55 mg) in an open-label manner. Data from this cohort indicate that single doses of SAGE-217 Oral Solution resulted in a reduction in the tremor symptoms, suggesting that SAGE-217 might be effective in treating PD.

There are no clinical efficacy data of SAGE-217 Oral Solution or Capsules in PD, since the present study is the first study in this indication.

5.4. Potential Risks and Benefits

Protocol 217-PRK-201 is the first clinical study evaluating the efficacy of SAGE-217 in PD. Thus, the potential benefits in this population are unknown, although the risks are likely to be similar to those mentioned in the Investigator's Brochure. GABA compounds that cross the blood-brain barrier or increase GABA activity alleviate muscle stiffness caused by a lack of GABAergic tone (Winkler 1999), validating this receptor as a therapeutic target. Given the promising clinical data with another neuroactive steroid (SAGE-547) in conjunction with the shared broad receptor selectivity profile, oral bioavailability, long half-life, preclinical evidence of anxiolytic activity, and safety data of SAGE-217, it is possible that patients may have a clinical benefit at the exposures selected for this study.

In the 217-CLP-103 study, SAGE-217 Capsules were found to be generally well-tolerated with no serious AEs reported during the treatment and follow-up periods. The most frequent AE observed was sedation that was mild, transient, and occurred within 1 to 4 hours following dosing and generally dissipated by 8 hours. The clinical portion of this study has recently completed; the final report is in progress.

In view of the few risks associated with administration of SAGE-217 that have been identified to date, intra-patient dose-reduction designs have been chosen for Part A and Part B to permit reduction in dose based on tolerability (adverse events), specifically sedation, versus treatment effect. In Part A, each subject will start with an initial dose of SAGE-217 Oral Solution, 30 mg; subjects unable to tolerate 30 mg will receive 20 mg; subjects unable to tolerate 20 mg will receive 10 mg. In Part B, each subject will receive SAGE-217 in the evening (PM) starting with an initial dose of SAGE-217 Capsules, 20 mg for two days; subjects able to tolerate 20 mg will receive 30 mg. If the subject is unable to tolerate 30 mg, the subject will receive 20 mg and continue for the remainder of the dosing period. Subjects who cannot tolerate the 20-mg dose at any time during Part B will be discontinued and replaced. The tolerated dose for each subject in Part A and Part B will be the dose taken on Day 7. Given the high medical need and potential for benefit in PD, there is a favorable benefit-risk evaluation to investigate SAGE-217 in PD.

In conclusion, selection criteria for the proposed study take into account the potential safety risks. Continuous safety monitoring, and the implementation of a formal dose-reduction and study drug discontinuation scheme also have the potential to mitigate risk. From a benefit/risk perspective, the appropriate measures are being taken in order to ensure the safety of the subjects who will be enrolled.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. 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 PD tremor symptoms.

6.2. 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.

6.3. Pharmacokinetic Objectives

The PK objective of Part A is:

- To assess the PK profile of SAGE-217 Oral Solution in plasma samples.

The PK objective of Part B is:

- To assess the PK profile of SAGE-217 Capsules utilizing a population PK approach.

6.4. Endpoints

6.4.1. Primary Endpoints

Part A:

- Frequency and severity of adverse events and changes 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 (SSS) score.

Part B:

- Improvement in PD tremor as assessed by changes in the MDS UPDRS Pa.ii II/ III tremor score (defined as the sum of MDS-UPDRS items 2.10, 3.15, 3.16, 3.17 and 3.18).

6.4.2. Secondary Endpoints

Part A:

- Improvement in PD motor symptoms as assessed by changes in the Movement Disorder Society-Unified Pai-Icinson's Disease Rating Scale (MDS-UPDRS) - Pa.ii III (Motor Examination) total score.

Part B:

- Improvement in PD motor symptoms as assessed by changes in the MDS-UPDRS - Pa.ii III total score.
- Improvement in PD nonmotor and motor aspects of experiences of daily living as assessed by the MDS-UPDRS - Pali I and Part II scores, respectively.
- Improvement in PD overall symptoms as assessed by changes in the MDS-UPDRS - Paiis I-IV total score.
- Frequency and severity of adverse events and changes in vital signs, clinical laboratory data, electrocai·diogram (ECG) parameters, and suicidal ideation using the Colllllllbia-Suicide Severity Rating Scale (C-SSRS).

6.4.3. Pharmacokinetic Endpoints

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

6.4.4. Exploratory Endpoints

I [redacted]

I [redacted]

I [redacted]

I [redacted]

I [redacted]

7. INVESTIGATIONAL PLAN

For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol.

7.1. Overall Study Design

This study is a two-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 Oral Solution for 4 days in 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 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 not eligible to participate in Part B. 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 of SAGE-217 Oral Solution (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 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 morning with food, as outlined in Section 9.1.1. 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). 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 (e.g., 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 (i.e., those who do not experience a severe adverse event 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 adverse event 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 outline in Section 9.1.2. 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.

The study designs of Part A and Part B are displayed in Figure 1 and Figure 2, respectively. Assessments will be performed periodically during the study as outlined in the Schedule of Events for Part A and Part B (Table 2 and Table 3, respectively).

7.2. Number of Subjects

Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14 to inform the conduct of Part B. Up to 15 new 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).

7.3. Treatment Assignment

SAGE-217 will be administered with food in Parts A and B. Food intake will be standardized as specified by the Sponsor. If subjects are taking antiparkinsonian agent(s), administration with or without food will be determined by the Investigator.

Parts A and B of the study are open-label. Dose reductions for lack of tolerability will be allowed during both parts of the study (Section 7.4).

7.4. Dose Adjustment Criteria

Dose reductions of SAGE-217 for lack of tolerability will be allowed during both parts of the study. If at any time the dose is not tolerated in Part A, as determined by the Investigator, the dose on the next day will be reduced to the next lowest dose (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). In Part B, subjects tolerating the initial 20-mg dose on Days 1 and 2 will receive a 30-mg dose on Day 3 and continue for the remainder of the dosing period. If on Day 3 or any time thereafter, the 30-mg dose is not tolerated, the dose on the next day must be reduced to 20 mg and continued for the remainder of the dosing period.

7.5. Criteria for Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons, including the occurrence of adverse events or other findings suggesting unacceptable risk to subjects, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their Institutional Review Board (IRB) and initiate withdrawal procedures for participating subjects.

Figure 1: Study Design of Part A

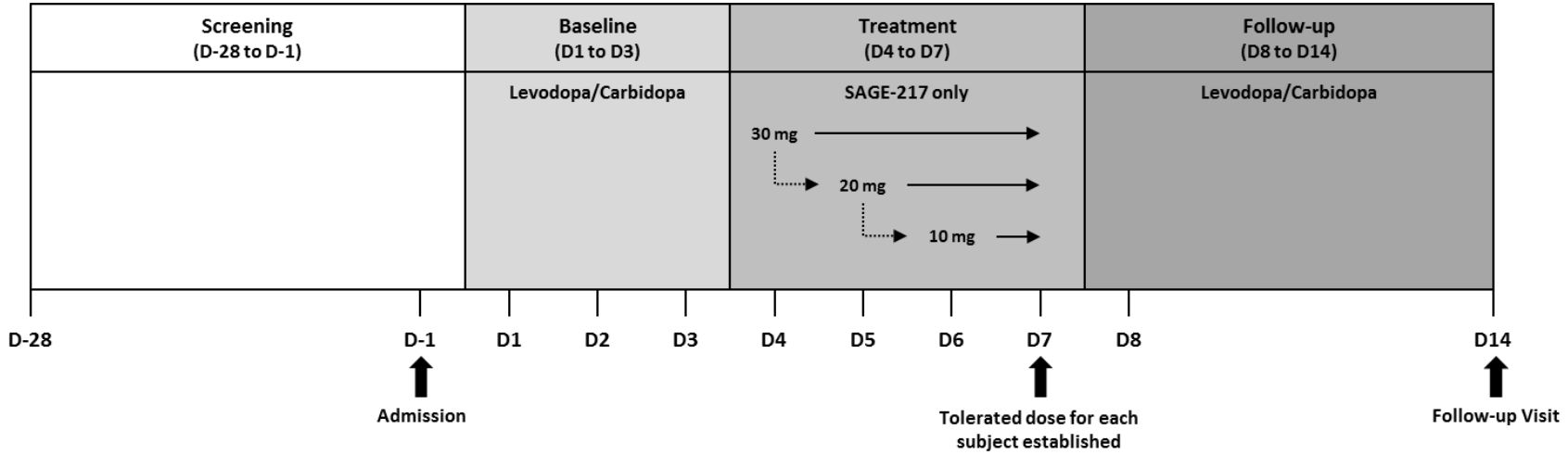
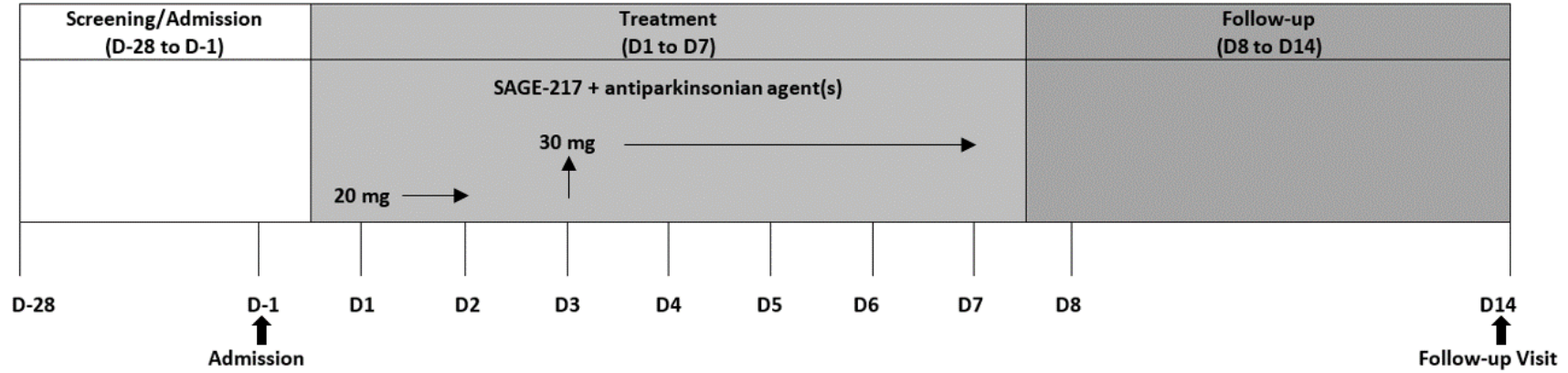


Figure 2: Study Design of Part B



NOTE: Part B will be initiated only after review of the Part A interim analysis (after 10 subjects have completed Part A).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

Subjects must meet the following inclusion criteria for enrollment in the study:

1. Subject has signed an informed consent form (ICF) before any study-specific procedures are performed.
2. Subject is between 40 and 75 years of age, inclusive.
3. Subject has a diagnosis of idiopathic PD based on modified UK Brain Bank Criteria (modified to allow individuals with a family history of PD) (Hughes 1992; Appendix 1).
4. **Part A**: Subjects with PD with a duration of less than 7 years and must meet the criteria for Hoehn and Yahr stage 2 or stage 3 (Appendix 2).

   Part B: Subjects with PD and must meet the criteria for Hoehn and Yahr stage 1-4 (Appendix 2) assessed during the "on" period (assumed to be within 2 hours of dosing with antiparkinsonian agent(s)), and have a tremor with a MDS-UPDRS Part II/III tremor score of ≥8 (sum of items: 2.10, 3.15, 3.16, 3.17 and 3.18) AND a MDS-UPDRS item score ≥3 in at least one limb (from items 3.15, 3.16, or 3.17). Inclusion criteria tremor scores must be assessed during "on" periods during the screening and Day -1 visit.
5. **Part A**: Subject has a stable dose of antiparkinsonian agent(s) including immediate-release oral Levodopa or Carbidopa-Levodopa (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.

   Part B: Subject is receiving a stable dose of antiparkinsonian agent(s) (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.
6. **Part A only**: Subject is willing to discontinue his/her treatment with immediate-release oral Levodopa or Carbidopa-Levodopa for at least 8 hours prior to dosing with SAGE-217.
7. **Part A**: Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) or amantadine at least 5 days prior to the day of admission (Day -1).

   Part B: Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) by Day -6 or amantadine by Day -10.
8. Subjects taking an antidepressant drug, sleep medication, or neuroleptic must have been on a stable dose for at least 1 month prior to the baseline visit.
9. Subjects must have a MoCA score of >22.
10. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests.
11. **Part A**: Female subjects must agree to practice a highly effective method of birth control while on study through completion of the last follow-up visit. If a subject discontinues

early after receiving a dose of SAGE-217, then the subject must continue this method of birth control for at least 7 days following the last dose of study drug. Highly effective methods of birth control include combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, or sexual abstinence.

Part B: Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause) and/or surgically sterile:

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception
- associated with inhibition of ovulation.
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner.
- Sexual abstinence (no sexual intercourse).

12. Male subjects must agree to practice a highly effective method of birth control while on study, and for 13 weeks after receiving the last dose of study drug. Effective methods of birth control include sexual abstinence, vasectomy, or a condom with spermicide (men) in combination with their partner's highly effective method.
13. Males must be willing to abstain from sperm donation and females from donating eggs while on study through 13 weeks after receiving the last dose of study drug.

8.2. Subject Exclusion Criteria

Subjects who met any of the following exclusion criteria will be excluded from the study:

1. Subjects with a known hypersensitivity to SAGE-217 Oral Solution or its major excipient, HPβCD (**Part A**) or SAGE-217 Capsule or its excipients (**Part B**).
2. **Part A**: Subjects with early PD (Hoehn and Yahr stage 1) or advanced PD (Hoehn and Yahr stage 4 or stage 5).

   Part B: Subjects with advanced PD (Hoehn and Yahr stage 5).
3. Subjects with any medical or psychiatric condition that jeopardizes/compromises his/her ability for participation. This includes schizophrenia spectrum and other psychotic disorders, substance-related and addictive disorders, feeding and eating disorders, bipolar

and related disorders, structural brain disease including but not limited to history of encephalitis or hydrocephalus and history of clinically significant stroke, or anticipating starting psychotherapy or behavior therapy during the course of the study, or who started psychotherapy or behavior therapy within 30 days prior to Day 1.

4. Subjects with a history of:
   a. Electroconvulsive therapy;
   b. Stereotaxic brain surgery (deep brain stimulation) for PD;
   c. History of suicide attempt within 2 years, or has answered YES to questions 3, 4, or 5 on the C-SSRS at the screening or Day -1 visits, or has current suicidal ideation; or
   d. Impulse control disorder.
5. **Part A only**: Subjects with severe depression as defined by a BDI-II score >19.
6. **Part B only**: Subject has recent exposure (14 days prior to the Day -1 visit) to tremorogenic drugs, as defined in Appendix 4.
7. Subjects with Type I or Type II diabetes mellitus.
8. Subjects with presence of drug-induced parkinsonism (eg, metoclopramide, flunarizine), metabolic identified neurogenetic disorders (eg, Wilson's disease), encephalitis, or other atypical Parkinsonian syndromes (eg, progressive supranuclear palsy, multiple system atrophy).
9. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.
10. Subject has clinically significant abnormal physical examination OR 12-lead ECG at the screening or admission visits. NOTE: QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study. ECG may be repeated once if initial values obtained are outside the specified limits.
11. Subject has a history, presence and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies 1 and 2.
12. Subject has exposure to another investigational medication or device within the prior 30 days.
13. Subject has donated one or more units of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing (1 unit = 450 mL).
14. Subject is unwilling or unable to comply with study procedures.
15. Subject has used any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.

8.3. Subject Withdrawal Criteria

Participation in the study is strictly voluntary. Subjects are free to discontinue the study at any time without giving their reason(s).

A subject must be withdrawn from the study treatment in the event of any of the following:

- Withdrawal of the subject's consent;
- New onset of a condition that would have met exclusion criterion, is clinically relevant and affects the subject's safety, and discontinuation is considered necessary by the Investigators and/Sponsor;
- Occurrence of intolerable adverse events;
- Occurrence of pregnancy;
- Intake of nonpermitted concomitant medication;
- Subject noncompliance;
- Significant protocol deviation determined in consultation with the Medical Monitor.

If a subject fails to attend scheduled assessments during the course of the study, the Investigators must determine the reasons and the circumstances as completely and accurately as possible and document this in the subject's source documents.

Subjects may be withdrawn from the study if there is concern for the subject's safety or it is determined that the subject is no longer a qualified participant. Subjects who cannot tolerate the 10-mg dose at any time during Part A or the 20-mg dose at any time during Part B will be withdrawn. Any subject who is withdrawn from the study for any reason is to have the final visit assessments performed.

Subjects who withdraw or are withdrawn from the study may be replaced.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug Treatment

For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol. All doses of SAGE-217 (Oral Solution or Capsule) will be administered with food.

9.1.1. Part A

Subjects participating in Part A of the study will take SAGE-217 Oral Solution in an open-label manner. 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 the following 3 days (Days 1 to 3). On the morning of Day 4, subjects will stop their immediate-release oral Levodopa and take SAGE-217 for 4 days (Days 4 to 7) in the AM with food. On Day 4, subjects will receive a 30 mg dose of SAGE-217. Subjects not tolerating 30 mg will receive 20 mg the next day, and subjects not tolerating 20 mg will receive 10 mg the next day. 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. Levodopa treatment will be resumed on Day 8 and continue through Day 14.

9.1.2. Part B

Subjects participating in Part B of the study will take SAGE-217 Capsules in an open-label manner. Subjects on a stable dose of antiparkinsonian agent(s) will continue taking them for the duration of the study. All subjects will receive SAGE-217, 20 mg, at 8PM on Days 1 and 2. On Day 3, subjects tolerating the initial dose (i.e., those who do not experience a severe adverse event judged by the Investigator to be related to study drug) will receive a dose increase (SAGE-217, 30 mg), at 8PM, 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 adverse event 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.

9.2. Concomitant Medications

9.2.1. Prior/Concomitant Medications

Any concomitant medication determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study under the guidance outlined in Section 9.2.

Record the name, start date (if known), indication for use and whether ongoing or stopped of medications/treatments taken within 2 weeks prior to study entry as well as any medications taken during the study.

The charts of all study participants will be reviewed for new concomitant medications through discharge from the unit. Chart reviews will include examination of nursing and physician progress notes, vital signs, and medication records in order to identify adverse events that may be associated with new concomitant medications. New concomitant medications, ongoing concomitant medications with a change in dose, and medical procedures ordered (eg, laboratory assessments, computed tomography or magnetic resonance imaging scans) will be reviewed to determine if they are associated with an adverse event not previously identified.

The Investigator will document all doses of Levodopa and Carbidopa-Levodopa taken by the subject and the use of rescue medication.

9.2.2. Prohibited Medications

Subjects who have used any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug are to be excluded from the study; these medications/products are prohibited during the study.

The anticholinergic drug classes listed in Appendix 3 are not permitted in the 5 days prior to the admission visit (Day -1) of Part A and Part B. The list provides non-exhaustive examples of each drug class.

Amantadine is not permitted in the 5 days prior to the admission visit of Part A or 9 days prior to the admission visit of Part B.

The tremorogenic drugs listed in Appendix 4 are not permitted in the 14 days prior to the admission visit of Part B.

9.3. Treatment Compliance

Study drug (SAGE-217 Oral Solution or Capsule) will be prepared by the site pharmacist. All doses of study drug will be administered by site staff while the subject is confined to the clinical unit. The Investigator(s) or designee will record the time and dose of study drug administration in the source documents. Any reasons for noncompliance will also be documented, including:

- Missing visits;
- Interruptions in the schedule of administration; and
- Nonpermitted medications.

The time at which study procedures are conducted should follow the protocol timelines as closely as possible.

9.4. Randomization and Blinding

Not applicable; Part A and Part B of the study are open-label.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

10.1.1. SAGE-217 Oral Solution

SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dosages. The 6 mg/mL stock SAGE-217 Oral Solution will be compounded from SAGE-217 Drug Substance Powder in the Bottle and Excipient(s) in the Bottle (manufactured under current Good Manufacturing Practice [GMP] conditions [redacted]) and further admixed at the clinical site in preparation for dosing. Detailed instructions for study drug preparation will be provided in the Pharmacy Manual.

The Sponsor will not provide Levodopa or Carbidopa-Levodopa during the study; subjects will use their prescribed Levodopa or Carbidopa-Levodopa.

10.1.2. SAGE-217 Capsule

SAGE-217 Capsules are available as hard gelatin capsules containing a white to off-white powder. In addition to the specified amount of SAGE-217 Drug Substance, active SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients. Capsules will be available in 5-mg, 10-mg and 20-mg dose strengths. Subjects will be administered two capsules per dose. Detailed instructions for study drug preparation will be provided in the Pharmacy Manual.

10.2. Study Drug Packaging and Labeling

The composition and pharmaceutical quality of the investigational product will be maintained according to the current GMP and Good Clinical Practice (GCP) guidelines and available for review in the study medication documentation. SAGE-217 Oral Solution will be provided to the site as powder in the bottle and excipient(s) in the bottle units to be compounded in the pharmacy at a volume of 125 mL of a 6 mg/mL stock solution and then further diluted to approximately 40 mL at the identified doses. SAGE-217 Capsules will be provided to the site in appropriately labeled bottles. Study drug labels with all required information and conforming to all applicable Code of Federal Regulations and GMP/GCP guidelines will be prepared by the clinical research organization.

10.3. Study Drug Storage

Upon receipt of study drug (SAGE-217), the Investigator or designee will inspect the materials and complete and return the acknowledgment of receipt form enclosed with the parcel. A copy of the signed receipt will be kept in the study files.

The study drug materials for SAGE-217 Oral Solution must be carefully stored at the temperature specified in the Pharmacy Manual (eg, clinical dosing solutions stored at approximately 2 to 8°C for 11 days with 24 hours of room temperature excursions allowed after preparation), safely and separately from other drugs. SAGE-217 Capsules may be stored at room temperature.

The study drug may not be used for any purpose other than the present study. After the study is completed, all unused study drug must be retained, returned as directed, or destroyed on site per the Sponsor's instructions.

The Investigator or designee will be responsible for ensuring appropriate storage, compounding, dispensing, inventory, and accountability of all clinical supplies. An accurate, timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory must be available for inspection by the designated representatives of the Sponsor or the Sponsor's representatives on request, and must include the information below:

- The identification of the subject to whom the drug was dispensed;
- The date(s) and quantity of the drug dispensed to the subject; and
- The product lot/batch number.

The preparation of the study drugs must be documented on a 'Drug Preparation and Dispensing Log Form' or similar form.

A copy of the inventory record and a record of any clinical supplies that have been destroyed must be documented. This documentation must include at least the information below or as agreed with the Sponsor:

- The number of prepared units;
- The number of administered units;
- The number of unused units;
- The number of units destroyed at the end of the study;
- The date, method, and location of destruction.

10.4. Study Drug Preparation

Each bottle of SAGE-217 Oral Solution 6 mg/mL will be compounded at the clinical pharmacy from components manufactured [redacted] and supplied by the Sponsor per the directions provided in the Pharmacy Manual. The batch formula for a 125 mL solution of the 6 mg/mL stock solution is shown in Table 5.

Table 5: Batch Formula for 125 mL of Stock SAGE-217 Oral Solution 6 mg/mL

Ingredient	Compendia Specification	Concentration (mg/mL)	Amount (mg/Bottle)
SAGE-217	not applicable	6	750
HPβCD [redacted]	USP/EP	457	57,100
Sucralose	USP/NF	0.025	3.124
Water for Injection	USP	not applicable	85,650

Abbreviations: EP = European Pharmacopeia; HPβCD = hydroxypropyl-β-cyclodextrin; NF = National Formulary; USP = United States Pharmacopeia

For the capsule formulation, subjects will swallow two capsules per dose with food.

10.5. Administration

SAGE-217 will be administered with food in the morning in Part A and in the evening in Part B.

Doses of SAGE-217 Oral Solution will be prepared as an approximate 40 mL oral solution to be swallowed all at once, followed by approximately 200 mL of water that has been used to rinse the dosing bottle. The start time of swallowing the approximately 40 mL oral solution is time zero for all assessments. Subjects may have assistance from the clinic staff when taking the study drug.

During Confinement, each subject's antiparkinsonian agents, including Levodopa or Carbidopa-Levodopa, will be administered by site personnel according to the site's standard operating procedures.

10.6. Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator or designee must maintain a record of all study drug received, used, and discarded.

The Sponsor will be permitted access to the study supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

The Investigator will document all doses of Levodopa or Carbidopa-Levodopa taken by the subject, including rescue doses.

10.7. Study Drug Handling and Disposal

The pharmacist or designee for drug accountability is to document the date and time of initial compounding (oral solution only), subsequent admixture of dosing solutions (oral solution only), administration of study drug, and for which subject the study drug was intended (ie, record subject initials and birth date or other unique identifier).

At the end of the study, any unused study drug will be retained or returned to the Sponsor for destruction or destroyed locally per the Sponsor's directions; disposition of study drug will be documented.

11. ASSESSMENT OF EFFICACY

Efficacy assessments include evaluation of PD symptoms by the MDS-UPDRS, [redacted] Assessments will be perfo1med periodicall y dming the study as outlined in the Schedule of Events for Pali A and Pali B (Table 2 and Table 3, respectively).

11.1. Movement Disorder Society- Unified Parkinson's Disease Rating Scale

The UPDRS is the most commonly used scale in clinical studies of PD (Ramaker 2002). In 2007, the MDS revised the scale, which was known as the MDS-UPDRS (Goetz 2007), and subsequently demonstrated the validity of the MDS-UPDRS for rating PD (Goetz 2008). The modified UPDRS includes fom scales, with various subscales. Each item is rated from 0 (no1m al) to 4 (severe) (Table 6). The fom MDS-UPDRS scales are:

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

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

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

Pait IV: Motor complications (6 items)

Table 6: Rating Scale for the MDS-UPDRS

Rating	Description
O = n 01mal	No symptoms /signs
1 = sligh t	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

Several questions in Pait I and all questions in Pait II can be answered by the patient/caregiver and completed without the Investigator's input. The remaining questions in Part I that deal with complex behaviors, the objective assessments of parkinsonism (Pait III), and the questions that deal with motor fluctuations and dyskinesias (Pait IV) ai·e co mpleted by In vestigator interview. The tim e requ ired for ad m inistering the MDS-UPDRS is estimated to be less than 10 minutes for the interview items of Pait I, 15 minutes for Pait III, and 5 minutes for Paii IV (Goetz 2008).
The complete MDS-UPDRS is to be administered in Pait A at screening, Admission (Day -1), on Day 8 prior to resuming Levodopa, and on Day 14. The complete MDS-UPDRS is to be administered in Pait B at screening, Admission (Day -1), in the morning of Days 1 and 8, and on Day 14. In both Paits A and B, the Admission (Day -1) complete MDS-UPDRS is perfo1med only if the time between Screening and Admission is ?:.7 days; othe1wise, the MDS-UPDRS Pait III only (Pait A) or Pait II and Pait III (Pait B) are perfo1med.

Pait II of the MDS-UPDRS assesses 13 categories of motor experiences of daily living: speech, salivation and drooling, chewing and swallowing, eating tasks, dressing, hygiene, handwriting,

doing hobbies and other activities, turning in bed, tremor, getting out of bed, car, or deep chair, walking and balance, and freezing (Goetz, 2008). Part II of the MDS-UPDRS (motor examination) is to be completed in Part B at 12 and 23 hours postdose on Days 1, 2, 3, 4, 5, and 6. If the complete MDS-UPDRS is not performed on Admission due to Admission taking place <7 days after Screening, then Part II should also take place on Admission (Day -1) for Part B.

Part III of the MDS-UPDRS assesses 18 motor categories, some of which include right and left measurements: speech, facial expression, kinetic tremor of hands, rest tremor ainplitude, 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, global spontaneity of movement (Goetz, 2008). Part III of the MDS-UPDRS (motor examination) is to be completed in Part A at 2, 4, 8, and 12 hours postdose on Days 1, 2, 3, 4, 5, 6, and 7. MDS-UPDRS is to be assessed within ±10 minutes of the scheduled times through the 4-hour time point and within ±15 minutes of the scheduled times for the 6-hour through 12-hour time points. Part III of the MDS-UPDRS (motor examination) is to be completed in Part B at 12 and 23 hours postdose on Days 1, 2, 3, 4, 5, and 6. If the complete MDS-UPDRS is not performed on Admission due to Admission taking place <7 days after Screening, then Part III should also take place on Admission (Day -1) for both Parts A and B.

All MDS-UPDRS measurements in Part B should be taken during the "on" period (within 2 hours of dosing with antiparkinsonian agent(s)).

The MDS-UPDRS is provided in Appendix 5.

11.2. Exploratory Endpoints

[redacted]

[redacted]

[redacted]

12. PHARMACOKINETICS

12.1. Blood Sample Collection

In Part A, plasma samples for PK analysis will be collected predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Day 4; predose on Day 5 and Day 6; predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Day 7; in AM of Day 8; and Day 14. Samples are to be collected within ±5 minutes of the scheduled sampling time.

In Part B, plasma samples for PK analysis will be collected predose and 13 hours postdose on Day 1; and 13 hours postdose on Days 2 through 7, and on Day 14. Samples are to be collected within ±1 hour of the scheduled sampling time.

The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. The Investigator or designee will arrange to have the plasma samples processed, stored, and transported as directed for bioanalysis.

An additional PK sample may be collected at any time if clinically indicated and at the discretion of the Investigator (eg, for unusual or severe adverse events).

Each sample will be marked with unique identifiers such as the study number, subject number, and the nominal sample time. The date and actual time that the blood sample was taken will be recorded on the eCRF or electronically with a bar code or other method.

12.2. Storage and Shipment of Pharmacokinetic Samples

The plasma samples should be kept frozen at approximately -70 to -80°C until analyzed. They should be packed as directed to avoid breakage during transit and with sufficient dry ice to prevent thawing for at least 72 hours. A specimen-identification form must be completed and sent to the laboratory with each set of samples. The clinical site will arrange to have the plasma samples transported as directed for bioanalysis as detailed in the PK instructions.

12.3. Sample Analysis

Bioanalysis of plasma samples for the determination of concentrations of SAGE-217 and possibly SAGE-217 metabolites will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory. Pharmacokinetic parameters will be derived such as area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), the distributional half-life and terminal half-life ($t_{½}$), and steady-state drug concentration in the plasma (C_{ss}).

13. ASSESSMENT OF SAFETY

13.1. Safety and Tolerability Parameters

Safety and tolerability of study drug will be evaluated by adverse event reporting, vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, and SSS (Part A only) and MOAA/S (Part A only) scores.

13.1.1. Demographic/Medical History

Age, gender, race, and ethnic origin will be recorded at the Screening visits. A full medical history, including PD history (e.g., time of diagnosis, Hoehn and Yahr staging) and medication history, will be recorded at the Screening visits.

13.1.2. Vital Signs

Vital signs comprise respiratory rate, temperature, and supine (supine for at least 5 minutes prior to the measurement) and standing systolic and diastolic blood pressure and heart rate.

Vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in AM of Day 8; and on Day 14. Vital signs and pulse oximetry are to be assessed within ±10 minutes of the scheduled times through the 4-hour time point and within ±15 minutes of the scheduled times for the 6-hour through 16-hour time points.

In Part B, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, and 12 hours postdose on Days 1 through 7; and on Day 14. Vital signs and pulse oximetry are to be assessed within ±10 minutes of the 1- and 2-hour time points and within ±15 minutes of the 12-hour time point.

13.1.3. Weight and Height

Body weight and height will be measured at the Screening visits for Parts A and B.

13.1.4. Physical Examination

A physical examination of all major body systems will be undertaken and recorded at the Screening visits for Parts A and B. Symptom-directed physical examinations will be performed during Part A on Admission (Day -1), Day 1, Day 3, Day 4, Day 6, and Day 8. Symptom-directed physical examinations will be performed during Part B on Admission (Day -1), Day 1, Day 3, Day 4, Day 6, and Day 8.

13.1.5. Electrocardiogram (ECG)

A supine 12-lead ECG will be performed at the times specified below and the standard intervals recorded as well as any abnormalities.

In Part A, the 12-lead ECG will be assessed at screening and Admission (Day -1); predose on Days 1 and 3; predose and 1 and 12 hours postdose on Days 4, 5, 6, and 7; in AM on Day 8; and Day 14. In Part B, the 12-lead ECG will be assessed at screening and Admission (Day -1); predose and 1 and 12 hours postdose on Days 1, 3, 5, and 7, and on Day 14.

All time points are relative to the time of dosing. ECGs are to be performed within ±10 minutes of the predose and 1-hour time points and within ±15 minutes of the 12-hour time point.

13.1.6. Laboratory Assessments

In Part A, blood samples will be collected for hematology and serum chemistry at the Screening visit, on Admission (Day -1), predose on Days 4, 6, and 8; and on Day 14. Urine samples will be collected in Part A at screening and Admission (Day -1); predose on Day 4 and Day 7; and on Day 14. In Part B, blood and urine samples will be collected at screening and Admission (Day -1); predose on Days 4 and 6; and on Day 8 and Day 14. On Day -1 of Part B, two blood samples will be taken: one sample will be sent to the central lab to be analyzed for reporting purposes and one sample is to be analyzed locally for study eligibility with regard to hematology/serum chemistry criteria.

Serum and urine samples for pregnancy tests (females only) will also be collected. These assessments should be performed in accordance with the Schedule of Events (Table 2 and Table 3 as outlined individually below.

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS). Screening results considered abnormal, CS recorded at the Screening visit may make the subject ineligible for the study pending review by the Medical Monitor. Clinical laboratory results that are abnormal, CS during the study but within normal range at baseline and/or indicate a worsening from baseline will be considered adverse events, assessed according to Section 13.2, and recorded in the eCRF.

13.1.6.1. Hematology

Hematology tests will include complete blood count (CBC), including red blood cells, white blood cells with differentiation, hemoglobin, hematocrit, reticulocytes, and platelets. The coagulation panel will include activated partial thromboplastin time, prothrombin time, and international normalized ratio.

13.1.6.2. Blood Chemistry

Serum chemistry tests will include serum electrolytes, renal function tests, including creatinine, blood urea nitrogen, bicarbonate or total carbon dioxide, liver function tests, including total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), alkaline phosphatase (Part B only), total protein, and albumin.

13.1.6.3. Urinalysis

Urinalysis will include assessment of protein, blood, glucose, ketones, bile, urobilinogen, hemoglobin, leukocyte esterase, nitrites, color, turbidity, pH, and specific gravity.

13.1.6.4. Virus Serology

Subjects will be screened for hepatitis (HBsAg and anti-HCV) and HIV prior to being enrolled in the study.

13.1.6.5. Pregnancy Screen

Females of childbearing potential will be tested for pregnancy at Parts A and B by serum pregnancy test at the Screening visits and by urine pregnancy test on Day -1 (Admissions). For Part B, females of childbearing potential will also be tested for pregnancy by urine pregnancy test at the follow-up visit on Day 14.

13.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS)

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

If in the opinion of the Investigator, the subject is showing any suicidal tendency, no further study drug will be administered and the subject will be referred to a psychologist or psychiatrist for further evaluation. This information will be tracked.

The "Baseline/Screening" C-SSRS form will be completed on Screening of Parts A and B (lifetime history and past 24 months). In Part A, the "Since Last Visit" C-SSRS form will be completed on Admission (Day -1); 12 hours postdose on Days 1, 2, and 3; predose on Days 4, 5, 6, and 7; and on Days 8 and 14. In Part B, the "Since Last Visit" C-SSRS form will be completed on Admission (Day -1); predose and 12 hours postdose on Day 1; 12 hours postdose on Days 2 through Day 7; and on Day 14. The C-SSRS is provided in Appendix 10.

13.1.8. Stanford Sleepiness Scale (SSS)

The SSS is 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'.

In Part A, the SSS will be administered on Admission (Day -1); predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in the AM on Day 8; and Day 14. All time points are relative to the time of dosing. 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. The SSS should be performed prior to the MOAA/S score. The SSS will not be administered in Part B. The SSS is provided in Appendix 11.

13.1.9. Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S)

The MOAA/S allows exploration of deeper sedation states than the SSS. If an 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. In Part A, the MOAA/S assessment should be conducted after other assessments that are scheduled at the same time point. In Part A, the MOAA/S will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 3, 4, 5, 6, and 7; in AM on Day 8; and Day 14. The MOAA/S will not be performed in Part B. The MOAA/S is provided in Appendix 12.

13.2. Adverse and Serious Adverse Events

Adverse events will be collected after the ICF has been signed. Medical conditions that occur after the ICF has been signed will be captured on the adverse event eCRF.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (version 18.1 or higher).

13.2.1. Definition of Adverse Events

13.2.1.1. Adverse Event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an adverse event can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All adverse events that occur after any subject has been enrolled, before treatment, during treatment, or following the cessation of treatment until the Day 14 Follow-up visit of Parts A and B, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics.

13.2.1.2. Suspected Adverse Reaction

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

13.2.1.3. Serious Adverse Event

A serious adverse event is an adverse event occurring during any study phase and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- It results in death
- It is immediately life-threatening
- It requires inpatient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- It results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

All serious adverse events that occur after any subject has been enrolled, before treatment, during treatment, and until the Day 14 Follow-up visit of Parts A and B, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics.

13.2.1.4. Recording Sedation as an Adverse Event

In Part A and Part B, sedation will be assessed using protocol-specified rating scales. Consideration should be given to the most appropriate term to describe the sedation characteristics.

For Part A, in order to standardize the reporting of sedation as adverse events, Investigators must record sedation as an adverse event if there is a score of >5 on the SSS and/or a score of ≤2 on the MOAA/S. SSS and MOAA/S do not apply to Part B.

13.2.2. Pregnancy

Any pregnancy occurring during this study will be reported within 24 hours of notification of the Investigator. The Investigator will promptly notify the Medical Monitor and withdraw the subject from the study. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The Investigator should request permission to contact the subject, the subject's spouse/partner (if the subject is male and his spouse/partner becomes pregnant) or the obstetrician for information about the outcome of the pregnancy (spontaneous miscarriage, elective termination, live birth), and in the case of a live birth, about any congenital abnormalities. If a congenital abnormality is reported, then it should be recorded in the source documents and reported as a serious adverse event. Spontaneous miscarriages should also be reported and handled as serious adverse events. Elective abortions without complications should not be handled as adverse events.

13.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each adverse event (unrelated, possibly related or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the adverse event should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the adverse event, then the adverse event should be considered "related."

Not related	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possibly related	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.
Probably related	The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.

If the relationship between the adverse event/serious adverse event and the investigational product is determined to be "possible" or "probable", the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

13.4. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as adverse events unless they prompt corrective medical action by the Investigator, constitute a serious adverse event or lead to discontinuation of administration of study drug.

Information about adverse events will be collected from the signing of the ICF until the final visit of the study for that subject. Adverse events that occur after the first administration of study drug will be denoted TEAEs.

All adverse events will be followed until they are resolved or have reached a clinical plateau with no expectation of future change.

The adverse event term should be reported in standard medical terminology when possible. For each adverse event, the Investigator will evaluate and report the onset (date and time), resolution or clinical plateau (date and time), intensity, causality, action taken, outcome, and whether or not it caused the subject to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe adverse events. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.2.1.3. An adverse event of severe intensity may not be considered serious.

13.5. Reporting Serious Adverse Events

All serious adverse events (regardless of causality) will be recorded from the signing of the ICF until the Day 14 Follow-up visit of Parts A and B. Any serious adverse events considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All serious adverse events must be reported to the Sponsor or Sponsor's designee immediately by phone and in writing within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the serious adverse event pages, verify the accuracy of the information recorded on the serious adverse event pages with the corresponding source documents, and send a copy to Sage Therapeutics or designee.

Additional follow-up information, if required or available, should be sent to Sage Therapeutics or designee within 24 hours of receipt; a follow-up serious adverse event form should be completed and placed with the original serious adverse event information and kept with the appropriate section of the CRF and/or study file.

Sage Therapeutics or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB of all serious adverse events that occur at his or her site if applicable per the IRB's requirements. Investigators

will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB of these additional serious adverse events.

14. STATISTICAL METHODS AND CONSIDERATIONS

14.1. Data Analysis Sets

The safety population is defined as all subjects who are administered at least one dose of study drug. Safety population will be used to provide descriptive summaries of all safety data.

The efficacy population will consist of all subjects in the safety population who receive at least one dose of study drug and have at least one postdose MDS-UPDRS evaluation. The efficacy population will be used to analyze all efficacy data.

The PK population will consist of all subjects in the safety population with sufficient plasma concentrations for PK evaluations.

Separate populations will be defined for each part of the study.

14.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. No imputation process will be used to estimate missing data. No sensitivity analysis of missing data will be performed.

14.3. General Considerations

For the purpose of all safety, efficacy, and exploratory analyses where applicable, baseline is defined as the last measurement prior to the start of study drug administration. Continuous endpoints will be summarized with n, mean, standard deviation (SD), median, minimum and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

14.4. Demographics and Baseline Characteristics

Demographics, such as age, gender, race, and ethnicity, and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized.

Categorical summaries, such as gender and race, will be summarized by frequency and percentage. Continuous summaries, such as age, height, weight, BMI, and baseline vital signs, will be summarized using descriptive statistics.

Hepatitis, 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 by subject.

14.5. Efficacy Endpoints

The primary endpoints of Part A relate to safety and tolerability. The primary endpoint for Part B is to evaluate the improvement in PD tremor as assessed by changes in the 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).

14.5.1. Secondary Efficacy Endpoints

fu Pait A, changes in the MDS-UPDRS- Pait III score will be Sllilllllaii·zed overall and by tolerated dose. fu Pait B, MDS-UPDRS Pali III total score, and the MDS-UPDRS - Pa.it s I- IV total score will be smmnai·ized overall and by and tolerated dose.

14.5.2. Exploratory Efficacy Endpoints

[redacted]

14.6. Safety and Tolerability Analyses

Data from vital signs, clinical laboratory measures, ECG, C-SSRS, SSS (Pa.ii A onl y), and MOAAIS (Pa11A only) will be smnmai·ized using descriptive statistics by group and time point, where applicable. Continuous endpoints will be Sllilllllai·izedwith nllllber (n), mean, standai·d deviation, median, minimllllll, and maximllllll. fu addition, change from baseline values will be calculated at each time point and will be smmnai·ized using descriptive statistics. Out-of-range safety endpoints may be categorized as low or high, where applicable. For all categorical endpoints, sUilllna ries wi ll include counts and percentages.

14.6.1. Adverse Events

Adverse events will be coded using the MedDRA coding system (version 18.1 or higher). The analysis of adverse events will be based on the concept of TEAEs. A TEAE is defined as an adverse event with onset after the start of open-label study drng, or any worsening of a pre-existing medical condition/adverseevent with onset after the strut of ope n-l abel study diu g and until 14 days after the last dose. The incidence of TEAEs will be sUillln ai·ized overall and by MedDRA System Organ Class, preferred tenn, and dose group. fucidences will be presented in order of decreasing frequency. fu addition, Sllilllllaii·es will be provided by maximllllll severity (see Section 13.4) and relationship to study diug (see Section 13.3).

Treatment-emergent adverse events leading to discontinuation and serious adverse events (see Section 13.2.1.3 for definition) with onset after the first dose of open-label study diug will also be sUillillaii·zed.

All adverse events and serious adverse events (including those with onset or worsening before the staii of open-label study diug) through the Day 14 Follow-up visit of Paii s A and B will be listed.

14.6.2. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from baseline of Pa.ii A and Pait B in vital signs will be evaluated by time point.

14.6.3. Physical Examinations

Screening physical examination results for Part A and Part B will be listed by subject. Any clinically significant physical examination will be recorded in medical history. Physical examination findings will be listed by subject and visit; abnormal findings will be flagged on the listing.

14.6.4. 12-Lead ECG

The following ECG parameters will be listed for each subject: heart rate, PR, QRS, QT, QTc, and QTcF. Any clinically significant abnormalities or changes in ECGs should be listed as an adverse event. Electrocardiogram findings will be listed by subject and visit.

14.6.5. Clinical Laboratory Evaluations

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline of Parts A and B in clinical laboratory measures will be summarized.

14.6.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality data collected on the C-SSRS will be listed for all subjects. Listings will include behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

14.6.7. Stanford Sleepiness Scale (SSS)

Sedation data collected on the SSS will be listed for all subjects in Part A. Changes in score over time will be represented graphically, and change from baseline of Part A will be summarized.

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

Sedation data collected on the MOAA/S will be listed for all subjects in Part A. Changes in score over time will be represented graphically, and change from baseline of Part A will be summarized.

14.6.9. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and will be coded using World Health Organization (WHO)-Drug dictionary September 2015, or later.

Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those taken during the 4 weeks prior to the date of the first dose of open-label study drug. Concomitant medications are defined as those with a start date on or after the first dose of open-label study drug, or those 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. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant. Details of prior and concomitant medications will be listed by study part, subject, start date, and verbatim term.

The use of rescue medication will be recorded and summarized.

14.7. Pharmacokinetic Analysis

Phaimacokinetic parameters will be Sllllirni.rized u s in g appropriate descriptive statistics. Time to reach maximllll concentration (tma.x) will be summarized using number (n), mean, standai·d deviation, median, minimllll, and maximllll. All other PK pai·ameters will be Sllillllarized using n, geometric mean, coefficient of vaii·ation, median, minimum, and maximllll and listed by subject.

Wherever necessaiy and appropriate, PK pai·ainetes will be dose-adjusted to account for individual differences in dose.

[redacted] Additional exposure-response analyses may be perfo1med for other measures of efficacy and safety.

14.8. Determination of Sample Size

Approximately 18 subjects will be enrolled in Pait A. An interim analysis is planned after 10 subjects have completed Pait A through Day 14. Up to 15 new subjects will be enrolled in Pait Bin order for 10 subjects to complete the study (tolerate at least 20 mg SAGE-217 for the duration of the dosing period). This number of subjects is thought to be sufficient to assess preliminaiy safety and tolerability as well as a signal of efficacy of SAGE-217 in subjects with PD.

14.9. Changes From Protocol Specified Analyses

Any changes from the analytical methods outlined in the protocol will be documented in the final statistical analysis plan.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of <Sponsor> will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sage Therapeutics or designee or its representatives. This will be documented in a Clinical Study Agreement between Sage Therapeutics and the Investigator.

During the study, a monitor from Sage Therapeutics or designee will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s);
- Confirm that facilities remain acceptable;
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts);
- Record and report any protocol deviations not previously sent to Sage Therapeutics or designee; and
- Confirm adverse events and serious adverse events have been properly documented on eCRFs and confirm any serious adverse events have been forwarded to Sage Therapeutics or designee and those serious adverse events that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

15.2. Audits and Inspections

Authorized representatives of Sage Therapeutics, a regulatory authority, an Independent Ethics Committee (IEC) or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sage Therapeutics or designee audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Council on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency about an inspection.

15.3. Institutional Review Board (IRB)

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator and institution will permit study-related monitoring, audits, IRB review, and regulatory inspections as requested by Food and Drug Administration, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (ie, original medical records, laboratory reports, hospital documents, progress reports, signed ICFs) in addition to eCRFs.

Quality assurance and quality-control systems with written standard operating procedures will be followed to ensure this study will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality-assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements made by the Sponsor with the Investigator/institution and any other parties involved with the clinical study will be in writing in a separate agreement.

17. ETHICS

17.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Sage Therapeutics or designee before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Sage Therapeutics or designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

17.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and the most recent amendment (2008) and are consistent with ICH/GCP and other applicable regulatory requirements.

17.3. Written Informed Consent

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

18. DATA HANDLING AND RECORDKEEPING

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

Electronic case report forms will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, and subject status.

The Investigator will have access to the electronic data capture system and will receive a copy of the subject eCRF data at the end of the study. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

18.1. Inspection of Records

Sage Therapeutics or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

18.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Sage Therapeutics or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18.3. Confidentiality

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available study registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used

towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

19. PUBLICATION POLICY

All information concerning SAGE-217 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

20. LIST OF REFERENCES

Belelli D, Casula A, Ling A, Lambert JJ. The influence of subunit composition on the interaction of neurosteroids with GABA(A) receptors. Neurophan nacology. 2002 Sep;43(4):651- 61.

[redacted]

Bergman H, Deuschl G. Pathophysiology of Parkinson's disease: from clinical neurology to basic neuroscience and back. Mov Disord. 2002;17:S28-S40.

[redacted]

di Michele F, Longone P, Romeo E, et al. Decreased plasma and cerebrospinal fluid content of neuroactive steroids in Parkinson's disease. Neurol Sci. 2003;24(3):172-3.

Goetz CG, Fahn S, Maitinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, fonnat, and clinimetric testing plan. Mov Disord. 2007;22(1):41-4 .

Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Pai·kinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov Disord. 2008;23(15):2129-70.

Hoehn M, Yahr M. Parkinsonism: onset, progression and mo1tality. Neurology. 1967;17(5):427-42.

[redacted]

Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Pai·kinson's disease. A clinico-pathological study of 100 cases. JNNP. 1992;55:181-4.

Jankovic J. Moto r fluctuations and dyskinesia in Parkinson's disease: Clinical manifestations. Mov Disord. 2005;11:ll -6.

Jankovic J. Parkinson's' disease: clinical features and diagnosis. JNNP. 2008;79:368-76.

Kasten M, Brnggemann N, Schmidt A, Klein C. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology. 2010;75 (5):478-9.

[redacted]

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatiy. 2011;168(12):1266-77.

Ramaker C, Marinus J, Stiggelbout AM, et al. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. Mov Disord. 2002;17(5):867- 76.

Siderowf A, Lang AE. Pre-motor Parkinson's disease; concepts and definitions. Mov. Disord 2012;27, 608-16.

Stem MB. Dopamine agonists modify the course of Parkinson disease. Arch Neurol. 2004;61:1969-71.

Weiner WJ. Initial treatment of Parkinson disease: levodopa or dopamine agonists. Arch Neurol. 2004;61:1966-9.

Winkler C, Bentlage C, Nikkhah G, et al. Intracranial transplants of GABA-rich striatal tissue induce behavioral recovely in the rat Parkinson model and promote the effects obtained by intrastriatal dopaminergic transplants. Exp. Neurol. 1999;155:165-186.

21. APPENDICES

Copies of scales and questionnaires included in the following appendices are for reference only; the rating scales and questionnaires reproduced in the eCRFs are to be used for actual subject assessment per the Schedule of Events.

APPENDIX 1. UNITED KINGDOM BRAIN BANK CRITERIA

UK PARKINSON'S DISEASE SOCIETY BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA*

Step 1. Diagnosis of Parkinsonian Syndrome

- Bradykinesia
- At least one of the following
  - Muscular rigidity
  - 4-6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease

- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

**From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181-184.*

APPENDIX 2. HOEHN AND YAHR STAGING CRITERIA

The Hoehn and Yahr scale, a commonly used system for describing how the symptoms of Parkinson's disease progress, was first published in 1967 (Hoehn 1967). The original scale included 5 disease stages, numbered 1 to 5.

Original Hoehn and Yahr Scale

Stage 1	Unilateral involvement only, usually with minimal or no functional disability
Stage 2	Bilateral or midline involvement without impairment of balance
Stage 3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent
Stage 4	Severely disabling disease; still able to walk or stand unassisted
Stage 5	Confinement to bed or wheelchair unless aided

APPENDIX 3. ANTICHOLINERGIC DRUGS

The following drugs are not permitted in the 5 days prior to receiving the first dose of study drug in Part A and Part B. The list below gives a non-exhaustive list of examples of each drug class.

A. Antimuscarinic agents

Atropine	Benzatropine	Biperiden	Chlorpheniramine
Dicyclomine	Dimenhydrinate	Diphenhydramine	Doxepin
Doxylamine	Glycopyrrolate	Hydroxyzine	Ipratropium
Orphenadrine	Oxitropium	Oxybutynin	Tolterodine
Tiotropium	Trihexyphenidyl	Scopolamine	Solifenacin
Tropicamide			

Tricyclic antidepressants (amitriptyline, clomipramine, doxepin, imipramine, trimipramine, amoxapine, desipramine, nortriptyline, protriptyline)

B. Antinicotinic agents:

Bupropion	Dextromethorphan	Doxacurium	Hexamethonium
Mecamylamine	Tubocurarine		

APPENDIX 4. TREMOROGENIC DRUGS

The following drug classes are not permitted in the 14 days prior to the Day -1 visit and for the duration of the study (up to the Day 14 visit). The list below gives a non-exhaustive list of examples of each drug class.

Anti-arrhythmics
amiodarone, procainamide

Antiepileptic drugs
valproic acid, carbamazepine

Antipsychotic agents
haloperidol, trifluoperazine

Antimanic agents/mood stabilizer
lithium at toxic levels

Antivirals
acyclovir, vidarabine

Beta adrenergic agonists
albuterol, terbutaline

Calcium Channel blockers
verapamil

CNS stimulants
methylphenidate, amphetamines, cocaine

Corticosteroids (local injection topical, or inhalation allowed)
cortisone, hydrocortisone, prednisone

Cytotoxic agents
cytarabine

Hormones
calcitonin, levothyroxine (levothyroxine is allowed if on a stable dose and euythroid)

Immunomodulatory
thalidomide

Immunosuppressants
cyclosporine, tacrolimus

Monoamine depleting agents
tetrabenazine

Oral hypoglycemic agents
metformin, glyburide, glipizide, tolbutamide, pioglitazone, rosiglitazone, acarbose, miglitol

Prokinetics
metoclopramide

Tricyclic antidepressants
amitriptyline, clomipramine, doxepin, imipramine, trimipramine, amoxapine, desipramine, nortriptyline, protriptyline

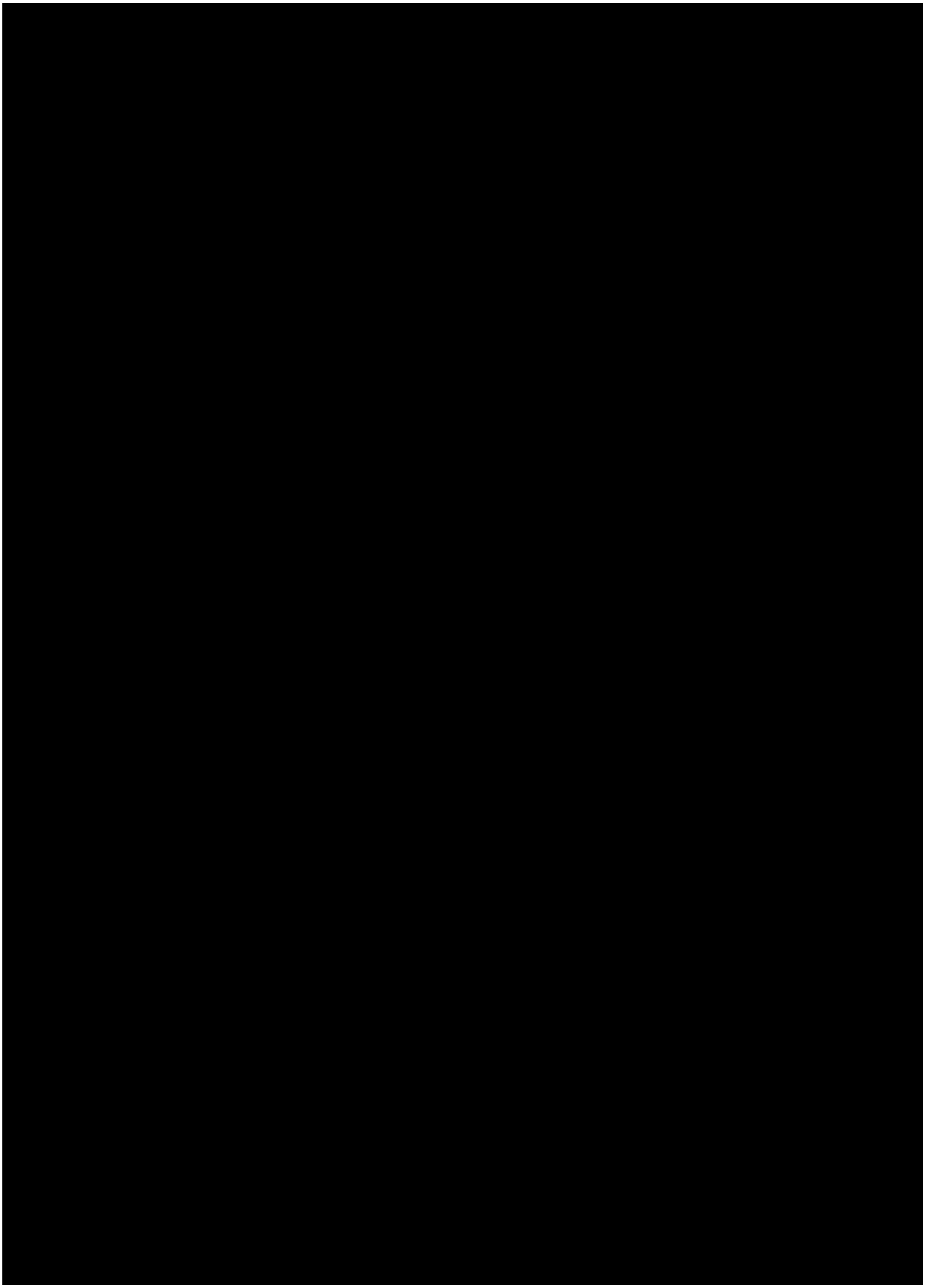
Selective Serotonin Reuptake Inhibitors (SSRIs)
fluoxetine (other SSRIs are allowed)

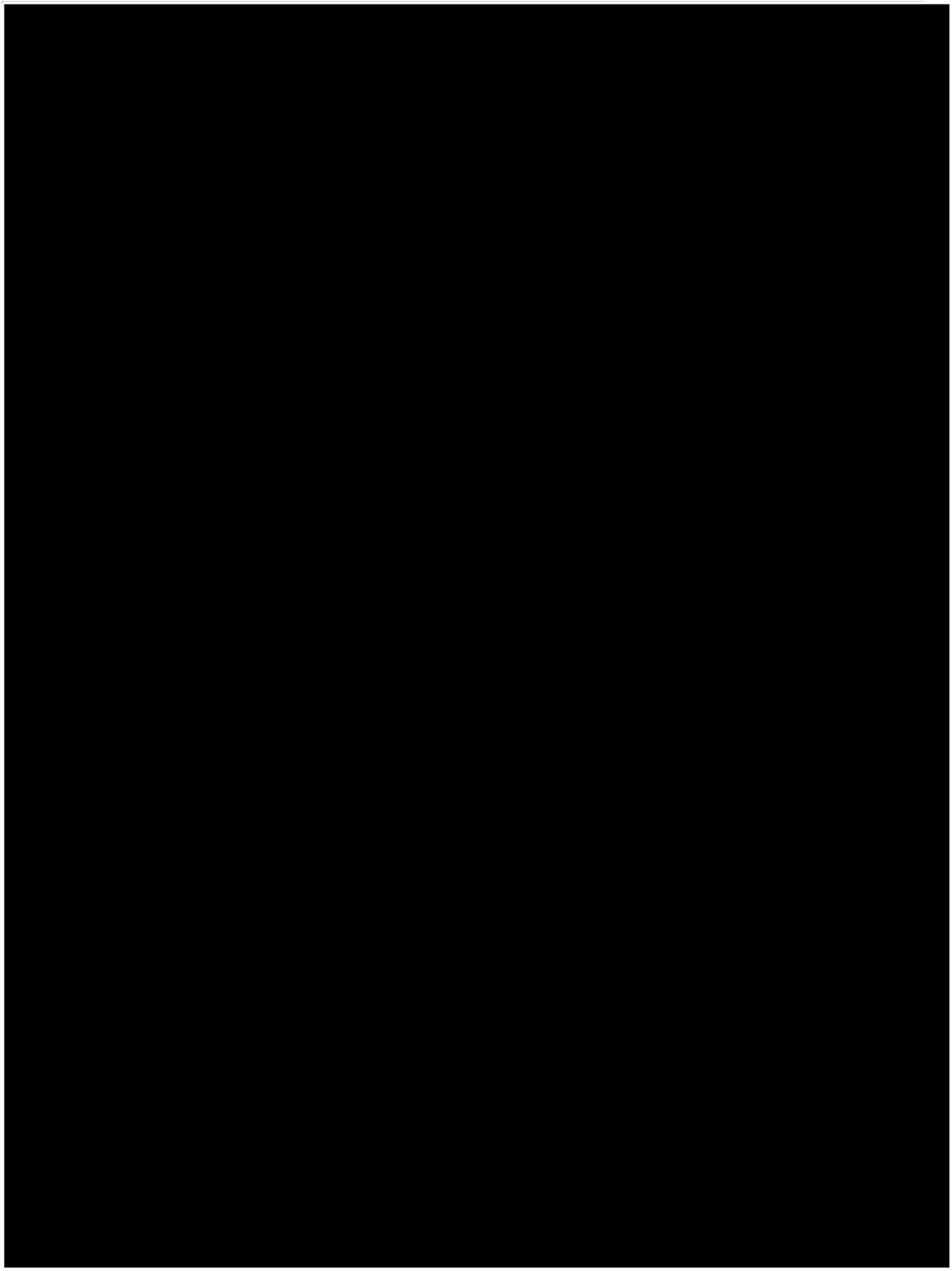
Statins
atorvastatin (other statins are allowed)

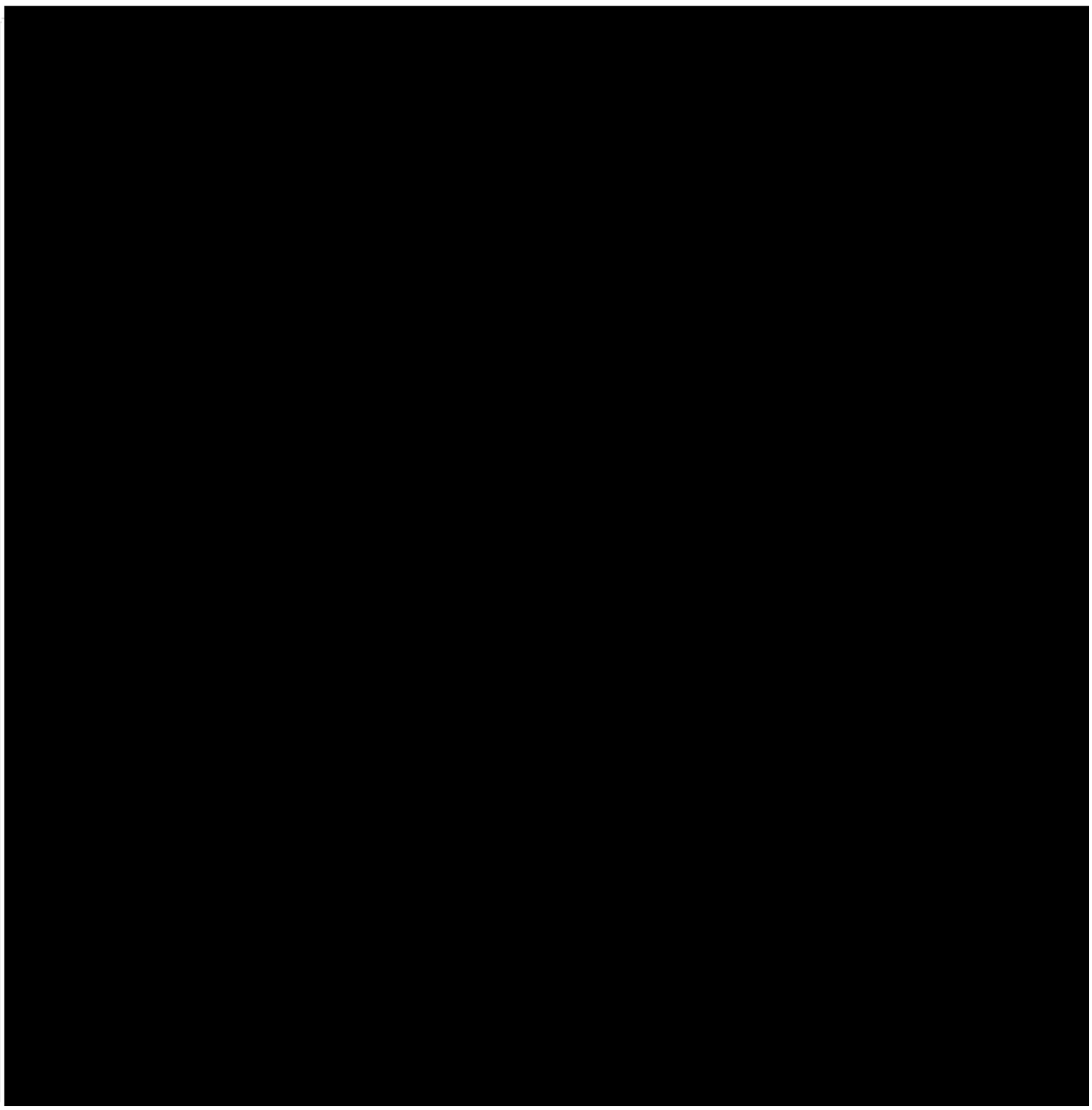
Sympathomimetics
epinephrine, pseudoephedrine
Weight loss medication
tiratricol
Xanthine derivatives
theophylline (caffeine/coffee and theophylline/theobromine/tea require a washout, cocoa beans are acceptable)

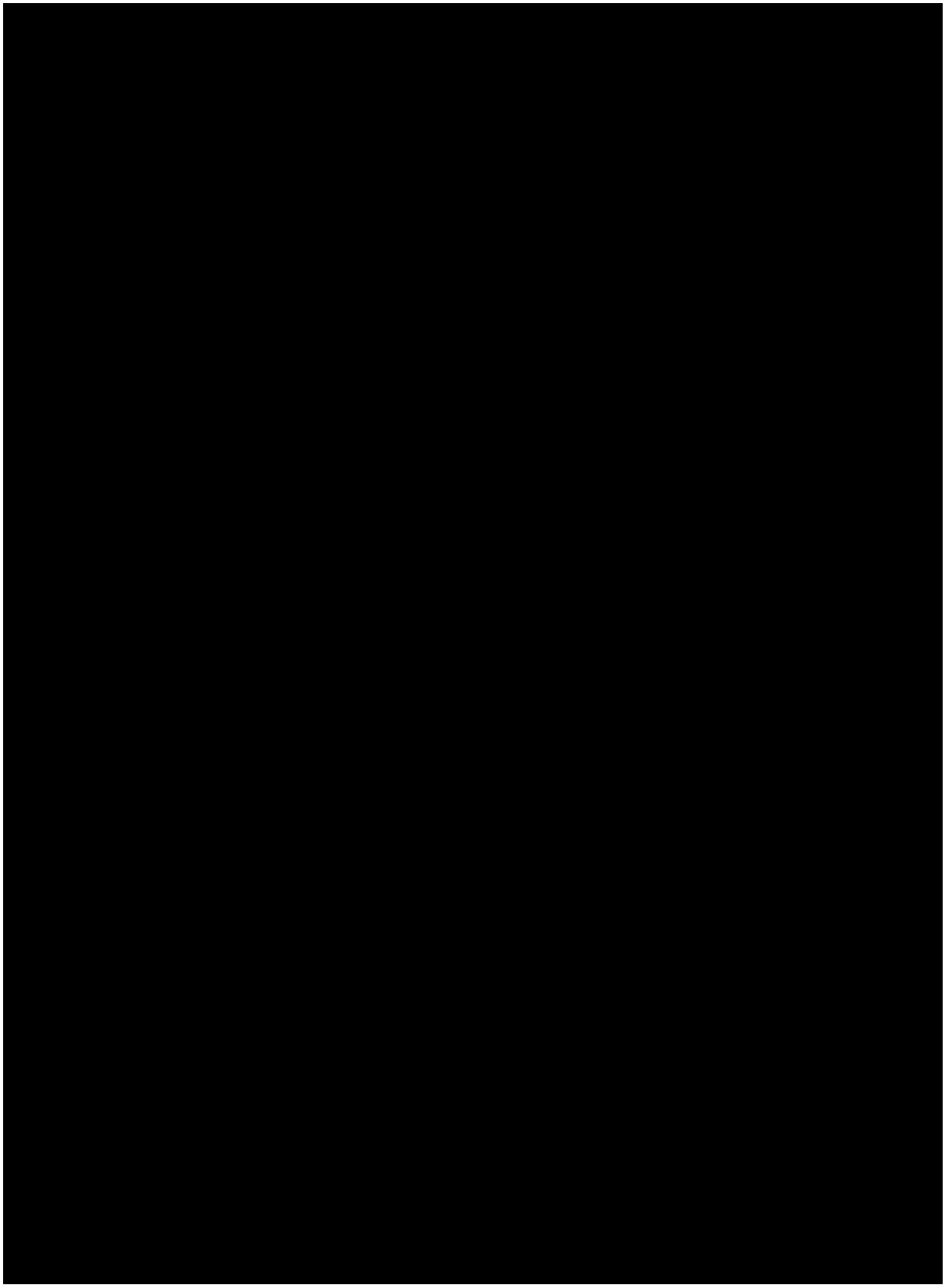
APPENDIX 5. MOVEMENT DISORDER SOCIETY-UNIFIED PARKINSON'S DISEASE RATING SCALE (MDS-UPDRS)

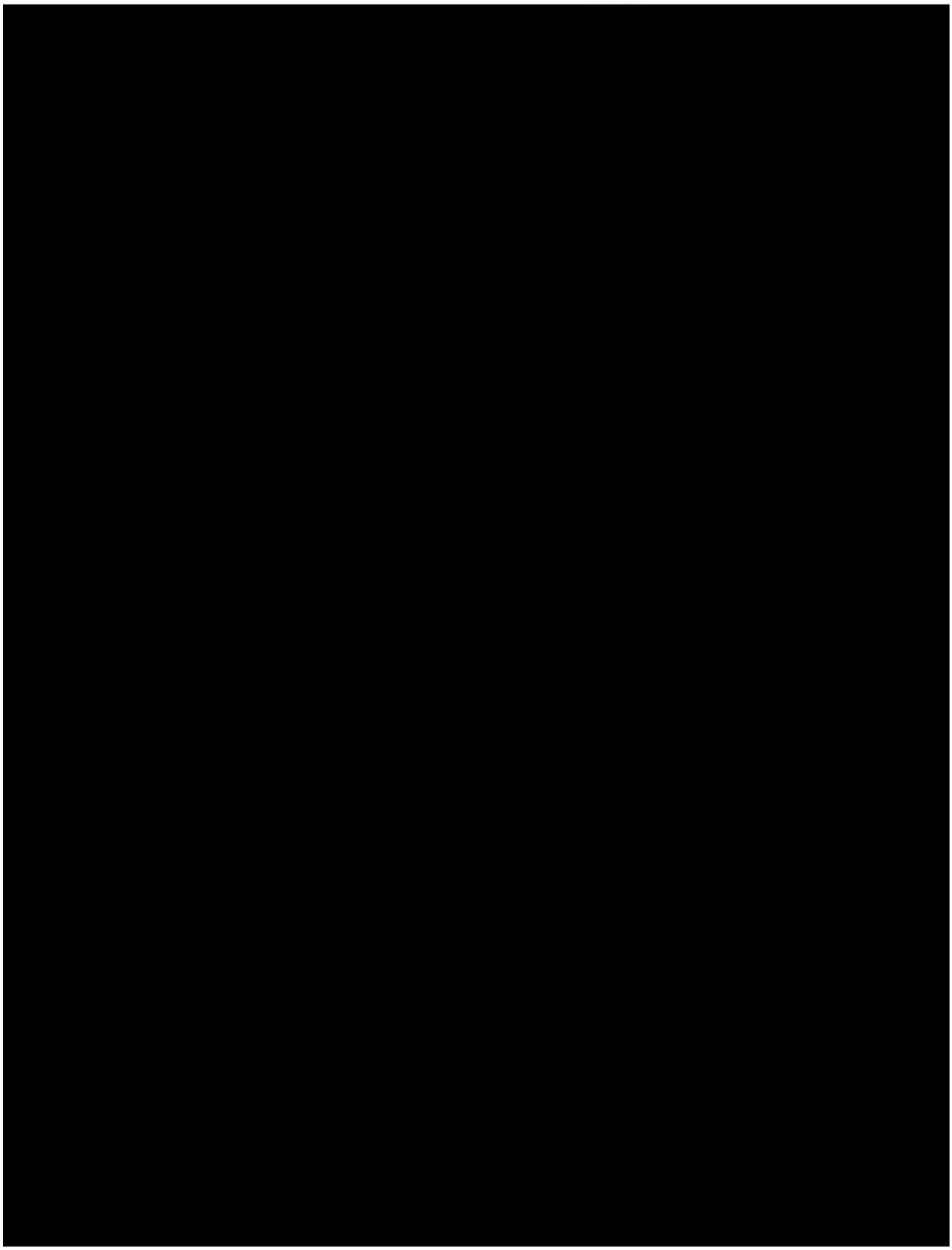
Part I: Nonmotor Aspects of Experiences of Daily Living	**Part II: Motor Experiences of Daily Living**
Cognitive impairment	Speech
Hallucinations and psychosis	Saliva and drooling
Depressed mood	Chewing and swallowing
Anxious mood	Eating tasks
Apathy	Dressing
Features of dopamine dysregulation syndrome	Hygiene
Sleep problems	Handwriting
Daytime sleepiness	Doing hobbies and other activities
Pain and other sensations	Turning in bed
Urinary problems	Tremor impact on activities
Constipation problems	Getting in and out of bed
Lightheadedness on standing	Walking and balance
Fatigue	Freezing
Part III: Motor Examination	**Part IV: Motor Complications**
Speech	Time spent with dyskinesias
Facial expression	Functional impact of dyskinesias
Rigidity (neck; right/left upper/lower extremities)	Painful *off* state dystonia
Finger tapping (right/left hands)	Time spent in the *off* state
Hand movements (right/left hands)	Functional impact of fluctuations
Pronation-supination movements of right/left hands	Complexity of motor functions
Toe tapping (right/left foot)	
Leg agility (right/left leg)	
Arising from chair	
Gait	
Freezing of gait	
Postural instability	
Posture	
Global spontaneity of movement (body bradykinesia)	
Postural tremor of right/left hands	
Kinetic tremor of right/left hands	
Rest tremor amplitude: right/left upper/lower extremities; lip jaw	
Constancy of rest tremor	

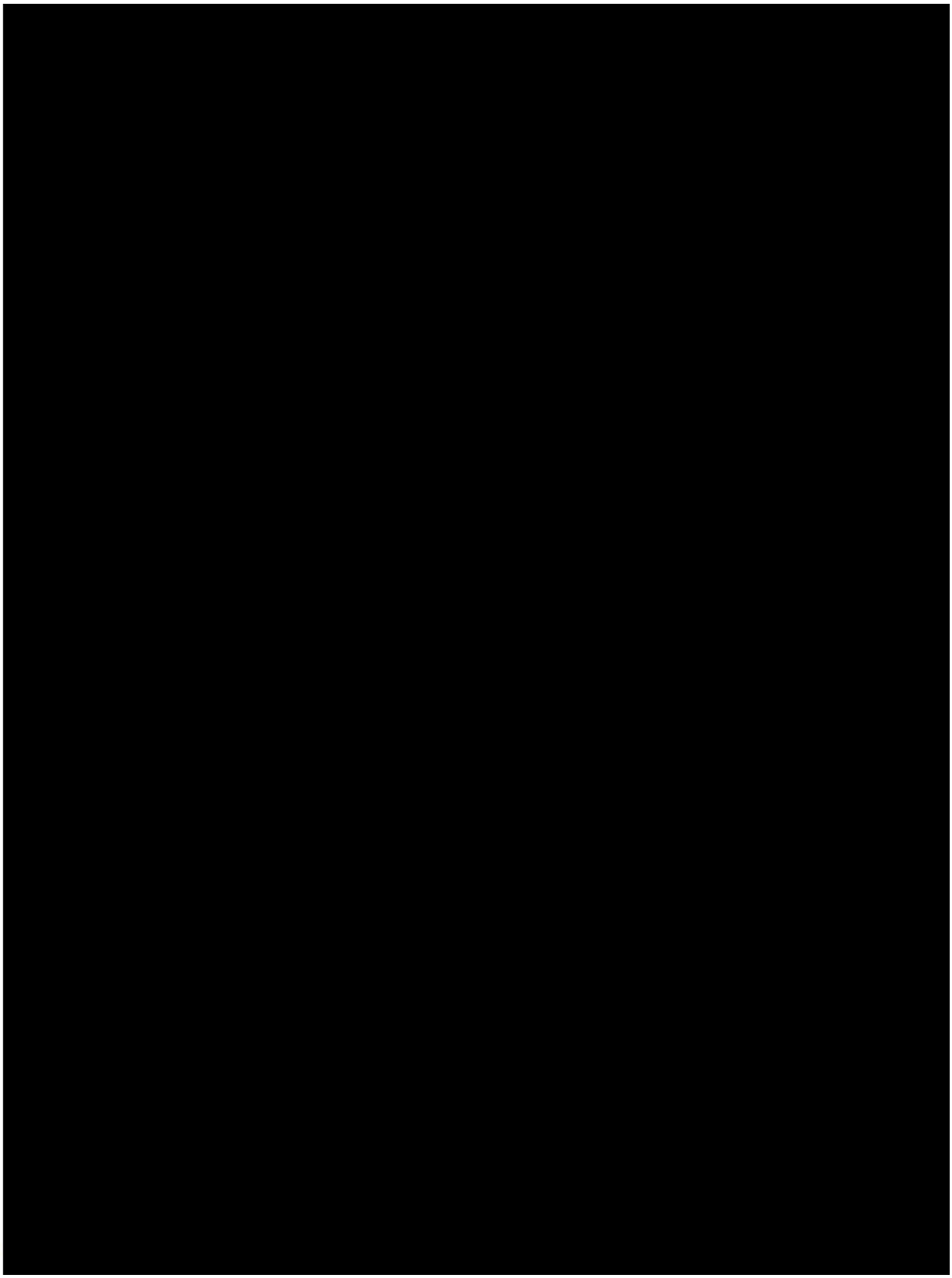


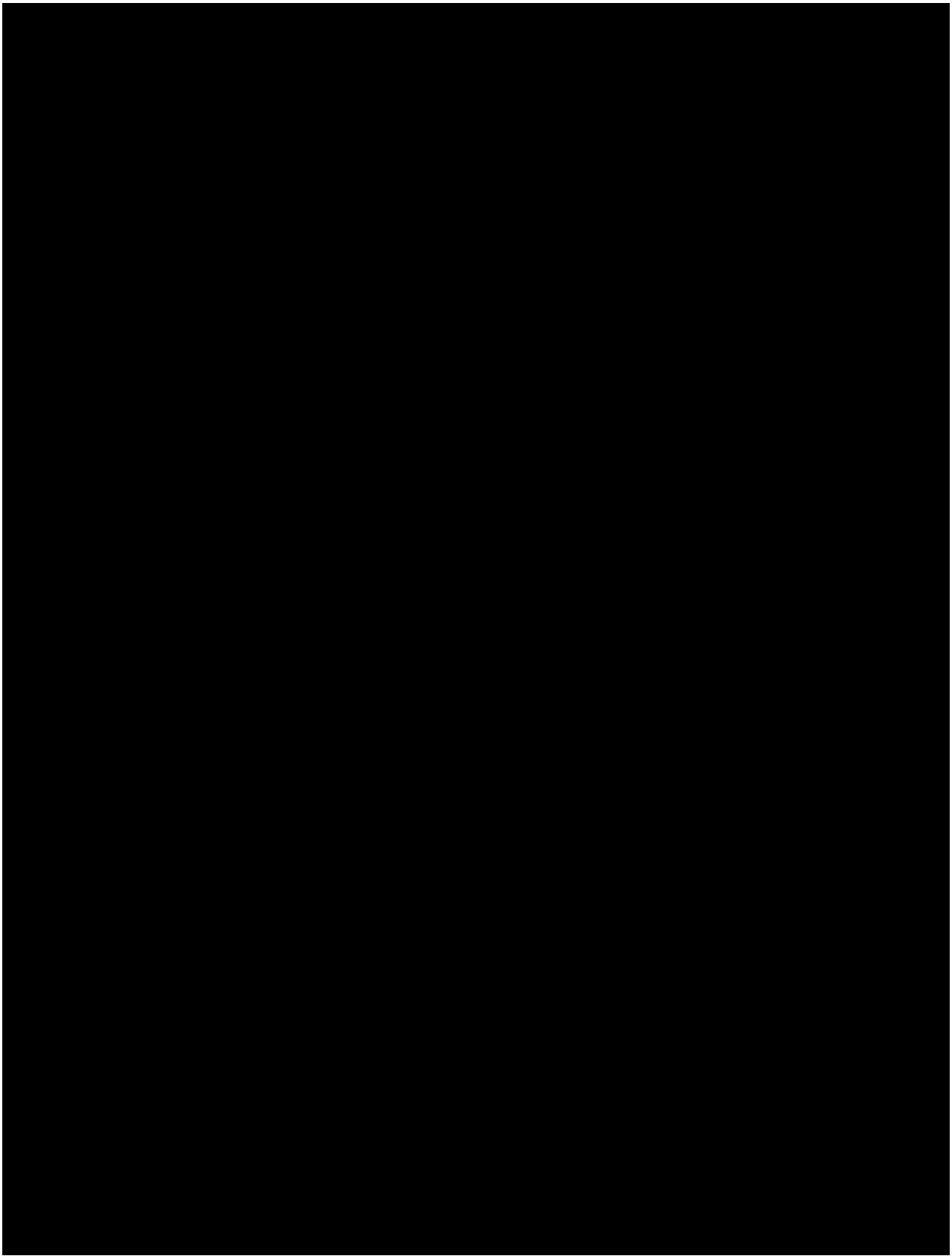


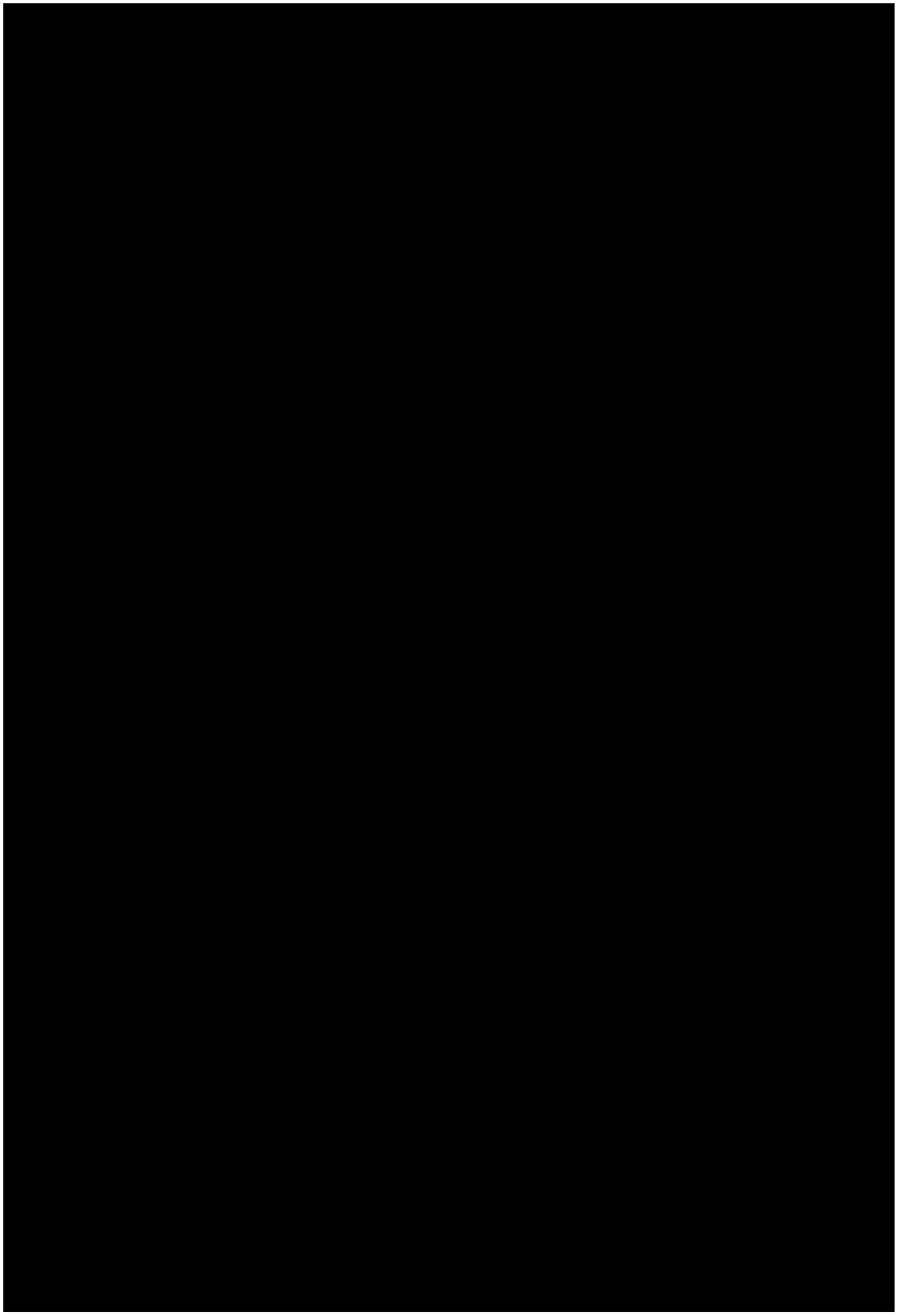


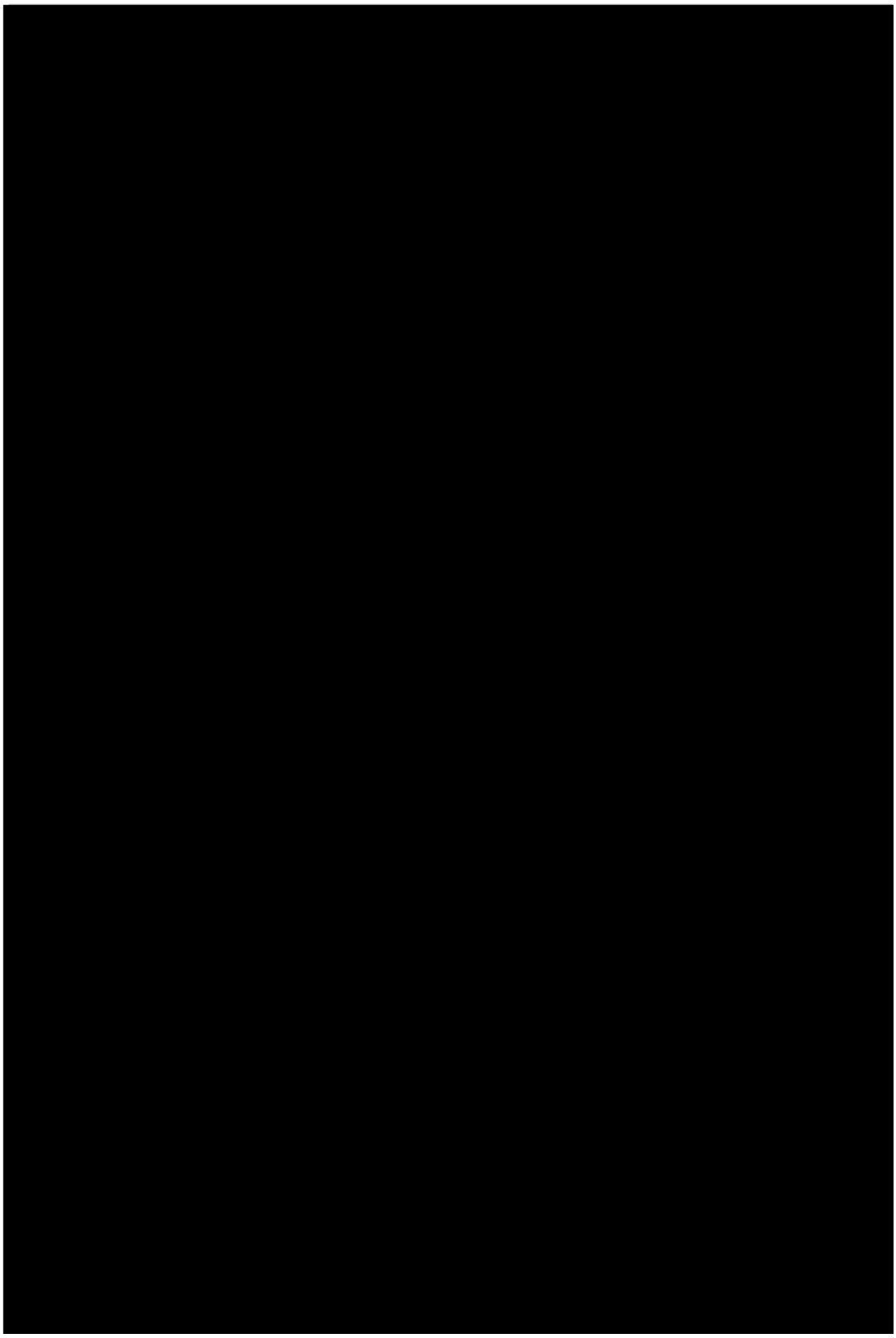












APPENDIX 10. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION AND SINCE LAST VISIT VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - *Most Severe Ideation:* _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - *Most Severe Ideation:* _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes No ☐ ☐ Total # of Attempts ____	Yes No ☐ ☐ Total # of Attempts ____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes No ☐ ☐	Yes No ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of interrupted ____	Yes No ☐ ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of aborted ____	Yes No ☐ ☐ Total # of aborted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes No ☐ ☐	Yes No ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes No ☐ ☐	Yes No ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

Yes ☐ No ☐

If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?

Yes ☐ No ☐

If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it....and I would never go through with it."*
Have you been thinking about how you might do this?

Yes ☐ No ☐

If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?

Yes ☐ No ☐

If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

Yes ☐ No ☐

If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX 11. STANFORD SLEEPINESS SCALE (SSS)

This is a quick way to assess how alert you are feeling. If it is during the day when you go about your business, ideally you would want a rating of a one. Take into account that most people have two peak times of alertness daily, at about 9 a.m. and 9 p.m. Alertness wanes to its lowest point at around 3 p.m.; after that it begins to build again. Rate your alertness at different times during the day. If you go below a three when you should be feeling alert, this is an indication that you have a serious sleep debt and you need more sleep.

An Introspective Measure of Sleepiness
The Stanford Sleepiness Scale (SSS)

Degree of Sleepiness	**Scale Rating**
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

APPENDIX 12. MODIFIED OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (MOAA/S)

Modified Observer's Assessment of Alertness/Sedation Scale

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Summary of Changes to
Protocol 217-PRK-201, Amendment #3
Date of Amendment: 06 June 2017

The following changes were made in Protocol 217-PRK-201 v4.0, Amendment #3. In addition, minor editorial revisions (eg, formatting, punctuation) that are not listed below may have been made throughout the protocol.

Section Number and Title	**Original Text:**	**Changed To:**	**Rationale:**
Document Header	Version 3.0 24 October 2016	**Amendment #3,** Version ~~3~~**4**.0 ~~24 October 2016~~ **CONFIDENTIAL**	Administrative update
Title Page, 2. Synopsis	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	A PHASE 2, TWO-PART STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND EFFICACY OF SAGE-217 ~~ORAL SOLUTION~~ IN ~~PATIENTS~~ **SUBJECTS** WITH PARKINSON'S DISEASE ~~OF MODERATE SEVERITY RESPONDING TO IMMEDIATE RELEASE ORAL LEVODOPA/CARBIDOPA AND WITHDRAWN FROM LEVODOPA/CARBIDOPA~~	a) With the addition of a capsule formulation, the study is no longer specific to SAGE-217 Oral Solution b) Update from 'Patients' to 'Subjects' to adhere to company style guide c) Part B inclusion criteria no longer considers disease severity and does not require withdrawal from levodopa/carbidopa
Title Page	Date of Amendment 2 Version 3.0, 24 October 2017	Date of Amendment 2 Version 3.0, 24 October 201~~7~~**6**	Correction

Section Number and Title	**Original Text:**	**Changed To:**	**Rationale:**
Title Page		**Date of Amendment 3 Version 4.0, 06 June 2017**	Administrative update
Protocol Signature Page	Product: SAGE-217 Oral Solution	Product: SAGE-217 ~~Oral Solution~~	With the addition of a capsule formulation, the study is no longer specific to SAGE-217 Oral Solution
Protocol Signature Page	Date of Amendment 2: Version 3.0, 24 October 2016	Date of Amendment ~~2~~**3**: Version ~~3~~**4**.0, ~~24 October 2017~~06 June 2017	Administrative update
Protocol Signature Page	[redacted], PhD [redacted] Sage Therapeutics	[redacted]~~, PhD~~ [redacted] **MS** [redacted] Sage Therapeutics	Administrative update
2. Synopsis, Name of Investigational Product	SAGE-217 Oral Solution	SAGE-217 Oral Solution **SAGE-217 Capsules**	Change made to accommodate the availability of a capsule formulation
2. Synopsis, Study centers	Up to 4 centers	Up to ~~4~~ **12** centers	Change made to accommodate more centers

Section Number and Title	Original Text:	Changed To:	Rationale:
2. Synopsis, Objectives	Primary: • To evaluate the safety and tolerability of SAGE-217 Oral Solution. Secondary: • 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. • To compare the effect of SAGE-217 Oral Solution in combination with immediate-release oral Levodopa/Carbidopa to Levodopa/Carbidopa alone.	Primary: **Part A:** • To evaluate the safety and tolerability of SAGE-217 Oral Solution. **Part B:** • **To evaluate the effect of SAGE-217 Capsules as an adjunct to antiparkinsonian agent(s) on the severity of PD tremor symptoms.** Secondary: **Part A**: • 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. • ~~To compare the effect of SAGE-217 Oral Solution in combination with immediate-release oral Levodopa/Carbidopa to Levodopa/Carbidopa alone.~~ **Part B:** • **To evaluate the effect of SAGE-217 Capsules as an adjunct to antiparkinsonian**	a) Changes made to divide the study objectives of Part A and Part B and make efficacy the primary objective for Part B; b) objectives added due to update of study design for Part B (randomized to open-label) and availability of SAGE-217 Capsule; c) added Pharmacokinetic objectives that were inadvertently missing from previous version

Section Number and Title	Original Text:	Changed To:	Rationale:
		agent(s) on motor and non-motor symptoms of PD. • **To evaluate the safety and tolerability of SAGE-217 Capsules.** **Pharmacokinetic:** • **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.**	
2. Synopsis, Endpoints	Primary: • Frequency and severity of adverse events and changes 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. Secondary: 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) score. Part B:	Primary: **Part A:** • Frequency and severity of adverse events and changes 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~~. **In addition, sleepiness/sedation as assessed by Stanford Sleepiness Scale (SSS) score.** **Part B:** • **Improvement in PD tremor as assessed by changes in the 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).**	a) Changes made due to division of study objectives between Part A and Part B; b) changes made due to update in study design for Part B

Section Nmnbe1· and Title	Original Text:	Changed To:	Rationale:
	Improvement in PD motor symptoms as assessed by changes in the MDS-UPDRS- Part III score. Improvement in PD overall symptoms as assessed by changes in the MDS-UPDRS - Parts I-IV total score. Sleepiness/sedation as assessed by the Stanford Sleepiness Scale (SSS) and Modified Observe r's Assessment of Analgesia/Sedation (MOAAIS) scores. In addition, plasma concentrations of SAGE-217 and possibly SAGE-217 metabolites will be measured, and pharmacokinetic (PK) parameters will be derived. Exploratory Endpoints: [redacted]	Secondaiy: Part A: Improvement in PD motor symptomsas assessed by changes in the Movement Disorder Society-Unified Par·kinson's Disease Rating Scale (MDS-UPDRS) - Part III (Motor Examination) score. Part B: • 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. • £kepi:Bess/seaatioa as assessed by tl½e S B:Bfot'd Sl@@ptn@ss Seal@(£££) end 4odifi@d Obse1ver's f.,ssessmeat of Analgesial£edatioa (MO,'\f.J£) scores. • **Frequency and severity of adverse events and changes in vital signs, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS).** **Pharmacokinetic:** • lB additioa, f)P lasma concentrations of SAGE-217,and possibly SAGE-217metabolites	

Section Nmnbe1· and Title	Original Text:	Changed To:	Rationale:
	[redacted]	will be measured, and f)liftfffi&eekiae ie (PKl parameters will be derived. **Exploratory** Endpoi:ras: [redacted]	

Section Nmnbe1· and Title	Original Text:	Changed To:	Rationale:
		[redacted]	
2. Synopsis, Methodology	This study will assess the safety, tolerability, PK, and efficacy of SAGE-217 Oral Solution. For ease of discussion, Levodopaalone or Carbidopa-Levodopacombination will be refened to as Levodopa in this protocol. Thereare two pa.its: Pait A: Open-label with morning (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 the following 3 days (Days 1 to 3). All subjects will stop their immediate-releaseoral Levodopa on Day 4 and will strut on a 30 mg dose of SAGE-217Oral Solution administered in the AM with food. Subjects not tolerating 30 mg will receive 20 mg, and subjectsnot tolerating 20 mg will receive 10 mg on subsequent days. The dose received on Day 7 will be defined as the tolerateddose for that subject.. Subjects not tolerating 10 mg will not be able to continue in	**Methodology:** This study will assess the safety, tolerability, **pharmaco kinetics** (PK) and efficacyeffectivenessof SAGE-2174fal. £elation. For ease of discussion, Levodopa alone or Carbidopa-Levodopacombination will be refened to as Levodopa in this protocol. There are two parts.;., **Part A and Part B, described below. Unique subjects will be enrolled in each part; subjects from Part A will *not* con tinue into Part B.** Pait A: Open-label with momiag (.'\Mt dosing (4 days). All subjects will continue to take their antiparkinsonian agent(s) including immediate-release oral Levodopa on the day of admission (Day -1) and in the AM only the following 3 days (Days1 to 3). All subjects will stop their immediate-releaseoral Levodopaon Day 4 and will strut on a 30 mg dose of SAGE-217 Oral Solution administeredin the AM with food.	Changes made due to update in study design for Pait B

Section Number and Title	Original Text:	Changed To:	Rationale:
	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 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 interim analysis. 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. Subjects randomized to the combination arm of Levodopa and SAGE-217 Oral Solution will receive this combination in the morning for the	Subjects not tolerating 30 mg will receive 20 mg, and subjects not tolerating 20 mg will receive 10 mg on subsequent days. 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 in order to inform the conduct of Part B. **Assessments will be performed periodically during the study as outlined in the Schedule of Events for Part A (Table 2).** 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 interim analysis.~~ ~~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~~	

Section Number and Title	Original Text:	Changed To:	Rationale:
	first 4 days (Days 1 to 4). Subjects randomized to the Levodopa plus placebo arm will receive Levodopa and SAGE-217 matching placebo oral solution 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). All doses of SAGE-217 Oral Solution (or placebo) will be administered in the morning with food. If subjects are taking Levodopa as opposed to Carbidopa-Levodopa, administration with or without food will be determined by the Investigator. 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 adverse event 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	~~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. Subjects randomized to the combination arm of Levodopa and SAGE 217 Oral Solution will receive this combination in the morning for the first 4 days (Days 1 to 4). Subjects randomized to the Levodopa plus placebo arm will receive Levodopa and SAGE 217 matching placebo oral solution 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).~~ ~~All doses of SAGE 217 Oral Solution (or placebo) will be administered in the morning with food. If subjects are taking Levodopa as opposed to Carbidopa Levodopa, administration with or without food will be determined by the Investigator.~~ ~~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,~~	

Section Number and Title	Original Text:	Changed To:	Rationale:
	A will be defined as 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 (Table 2 and Table 3, respectively).	~~assessed by occurrence of a severe adverse event 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 defined as 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.~~ **Open-label with evening (PM) dosing, 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**	

Section Number and Title	Original Text:	Changed To:	Rationale:
		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 adverse event 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 adverse event 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. 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~~s A~~ and B (~~Table 2 and~~ Table 3~~, respectively~~).	

Section Number and Title	**Original Text:**	**Changed To:**	**Rationale:**
2. Synopsis, Number of patients (planned)	Number patients (planned)	Number ~~patients~~ **subjects** (planned)	Administrative update
2. Synopsis, Number of patients (planned), 7.2. Number of Subjects	Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14 to inform the conduct of Part B. Twelve subjects are anticipated to be randomized in Part B.	Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14 to inform the conduct of Part B. ~~Twelve subjects are anticipated to be randomized in Part B.~~ **Up to 15 new 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).**	Changes made due to update in study design for Part B
2. Synopsis, Diagnosis and main criteria for inclusion	Diagnosis and main criteria for inclusion: All of the following inclusion and exclusion criteria will be applied during screening for Part A, with some of the criteria applied during screening for Part B, as indicated.	~~Diagnosis and main criteria for inclusion: All of the following inclusion and exclusion criteria will be applied during screening for Part A, with some of the criteria applied during screening for Part B, as indicated.~~	Changes made due to update in study design for Part B
2. Synopsis, Diagnosis and main criteria for inclusion, 8.1. Subject Inclusion Criteria	1. Subject has signed an informed consent form (ICF) before any study-specific procedures are performed. 2. Subject is between 40 and 75 years of age, inclusive. 3. Subject has a diagnosis of idiopathic PD based on modified UK Brain Bank Criteria (modified to allow individuals with a family history of PD) (Hughes 1992; Appendix 1).	1. Subject has signed an informed consent form (ICF) before any study-specific procedures are performed. 2. Subject is between 40 and 75 years of age, inclusive. 3. Subject has a diagnosis of idiopathic PD based on modified UK Brain Bank Criteria (modified to allow individuals with a family history of PD) (Hughes 1992; Appendix 1).	Changes made to distinguish criteria for Part A and Part B and due to updated study design for Part B

Section Number and Title	Original Text:	Changed To:	Rationale:
	4. Subjects with PD with a duration of less than 7 years and must meet the criteria for Hoehn and Yahr stage 2 or stage 3 (Appendix 2). 5. Subject has a stable dose of antiparkinsonian agents including immediate-release oral Levodopa or Carbidopa-Levodopa (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study. 6. Subject is willing to discontinue his/her treatment with immediate-release oral Levodopa or Carbidopa-Levodopa for at least 8 hours prior to dosing with SAGE-217. (Part B also) 7. Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) or amantadine at least 5 days prior to the day of admission (Day -1). (Part B also) 8. Subjects taking an antidepressant drug, sleep medication, or neuroleptic must have been on a stable dose for at least 1 month prior to the baseline visit. 9. Subjects must have a MoCA score of >22. 10. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests. (Part B also)	4. **Part A:** Subjects with PD with a duration of less than 7 years and must meet the criteria for Hoehn and Yahr stage 2 or stage 3 (Appendix 2). **Part B: Subjects with PD and must meet the criteria for Hoehn and Yahr stage 1-4 (Appendix 2) assessed during the "on" period (assumed to be within 2 hours of dosing with antiparkinsonian agent(s)), and have a tremor with a MDS-UPDRS Part II/III tremor score of ≥8 (sum of items: 2.10, 3.15, 3.16, 3.17 and 3.18) AND a MDS-UPDRS item score ≥3 in at least one limb (from items 3.15, 3.16, or 3.17). Inclusion criteria tremor scores must be assessed during "on" periods during the screening and Day -1 visit.** 5. **Part A:** Subject has a stable dose of antiparkinsonian agent(s) including immediate-release oral Levodopa or Carbidopa-Levodopa (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study. **Part B: Subject is receiving a stable dose of antiparkinsonian agent(s) (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.** 6. **Part A only:** Subject is willing to discontinue his/her treatment with immediate-release oral	

Section Number and Title	Original Text:	Changed To:	Rationale:
	11. Female subjects must agree to practice a highly effective method of birth control while on study through completion of the last follow-up visit. If a subject discontinues early after receiving a dose of SAGE-217, then the subject must continue this method of birth control for at least 7 days following the last dose of study drug. Highly effective methods of birth control include combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence. (Part B also) 12. Male subjects must agree to practice a highly effective method of birth control while on study, and for 13 weeks after receiving the last dose of study drug. Effective methods of birth control include sexual abstinence, vasectomy, or a condom with spermicide (men) in combination with their partner's highly effective method. (Part B also) 13. Males must be willing to abstain from sperm donation and females from donating eggs while on study through 13 weeks after receiving the last dose of study drug. (Part B also)	Levodopa or Carbidopa-Levodopa for at least 8 hours prior to dosing with SAGE-217. ~~(Part B also)~~ 7. **Part A:** Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) or amantadine at least 5 days prior to the day of admission (Day -1). ~~(Part B also)~~ **Part B: Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) by Day -6 or amantadine by Day -10.** 8. Subjects taking an antidepressant drug, sleep medication, or neuroleptic must have been on a stable dose for at least 1 month prior to the baseline visit. 9. Subjects must have a MoCA score of >22. 10. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests. ~~(Part B also)~~ 11. **Part A:** Female subjects must agree to practice a highly effective method of birth control while on study through completion of the last follow-up visit. If a subject discontinues early after receiving a dose of SAGE-217, then the subject must continue this method of birth control for at least 7 days following the last dose of study drug. Highly effective methods of birth control include combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with	

Section Number and Title	Original Text:	Changed To:	Rationale:
		inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence. ~~(Part B also)~~ **Part B: Female subject agrees to use one of the following methods of contraception during participation in the study and for 30 days following the last dose of study drug, unless they are postmenopausal (defined as no menses for 12 months without an alternative medical cause) and/or surgically sterile:** • **Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception** • **associated with inhibition of ovulation.** • **Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation.** • **Intrauterine device.** • **Intrauterine hormone-releasing system.** • **Bilateral tubal occlusion.** • **Vasectomized partner.** • **Sexual abstinence (no sexual intercourse).** 12. Male subjects must agree to practice a highly effective method of birth control while on study, and for 13 weeks after receiving the last dose of study	

Section Number and Title	Original Text:	Changed To:	Rationale:
		drug. Effective methods of birth control include sexual abstinence, vasectomy, or a condom with spermicide (men) in combination with their partner's highly effective method. ~~(Part B also)~~ 13. Males must be willing to abstain from sperm donation and females from donating eggs while on study through 13 weeks after receiving the last dose of study drug. ~~(Part B also)~~	
2. Synopsis, Exclusion criteria, 8.2. Subject Exclusion Criteria	1. Subjects with a known hypersensitivity to SAGE-217 Oral Solution or its major excipient, HPβCD. (Part B also) 2. Subjects with early PD (Hoehn and Yahr stage 1) or advanced PD (Hoehn and Yahr stage 4 or stage 5). 3. Subjects with any medical or psychiatric condition that jeopardizes/compromises his/her ability for participation. This includes schizophrenia spectrum and other psychotic disorders, substance-related and addictive disorders, feeding and eating disorders, bipolar and related disorders, structural brain disease including but not limited to history of encephalitis or hydrocephalus and history of clinically significant stroke, or anticipating starting psychotherapy or behavior therapy during the course of the study or who started psychotherapy or behavior therapy within 30 days prior to Part A Day 1.	1. Subjects with a known hypersensitivity to SAGE-217 Oral Solution or its major excipient, HPβCD. (**Part A) or SAGE-217 Capsule or its excipients Part B** ~~also~~) 2. **Part A:** Subjects with early PD (Hoehn and Yahr stage 1) or advanced PD (Hoehn and Yahr stage 4 or stage 5). **Part B: Subjects with advanced PD (Hoehn and Yahr stage 5).** 3. Subjects with any medical or psychiatric condition that jeopardizes/compromises his/her ability for participation. This includes schizophrenia spectrum and other psychotic disorders, substance-related and addictive disorders, feeding and eating disorders, bipolar and related disorders, structural brain disease including but not limited to history of encephalitis or hydrocephalus and history of clinically significant stroke, or anticipating starting psychotherapy or behavior therapy during the course	Changes made to distinguish criteria for Part A and Part B and due to updated study design for Part B

Section Number and Title	Original Text:	Changed To:	Rationale:
	4. Subjects with a history of: a. Electroconvulsive therapy; b. Stereotaxic brain surgery (deep brain stimulation) for PD; c. History of suicide attempt within 2 years, or has answered YES to questions 3, 4, or 5 on the C SSRS at the screening or Day -1 visits, or has current suicidal ideation; or d. Impulse control disorder. 5. Subjects with severe depression as defined by a BDI-II score >19. 6. Subjects with Type I or Type II diabetes mellitus. 7. Subjects with presence of drug-induced parkinsonism (eg, metoclopramide, flunarizine), metabolic identified neurogenetic disorders (eg, Wilson's disease), encephalitis, or other atypical Parkinsonian syndromes (eg, progressive supranuclear palsy, multiple system atrophy). (Part B also) 8. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease. (Part B also)	of the study or who started psychotherapy or behavior therapy within 30 days prior to ~~Part A~~ Day 1. 4. Subjects with a history of: a. Electroconvulsive therapy; b. Stereotaxic brain surgery (deep brain stimulation) for PD; c. History of suicide attempt within 2 years, or has answered YES to questions 3, 4, or 5 on the C SSRS at the screening or Day -1 visits, or has current suicidal ideation; or d. Impulse control disorder. 5. **Part A:** Subjects with severe depression as defined by a BDI-II score >19. **6. Part B: Subject has recent exposure (14 days prior to the Day -1 visit) to tremorogenic drugs, as defined in Appendix 4.** ~~6~~**7**. Subjects with Type I or Type II diabetes mellitus. ~~7~~**8**. Subjects with presence of drug-induced parkinsonism (eg, metoclopramide, flunarizine), metabolic identified neurogenetic disorders (eg, Wilson's disease), encephalitis, or other atypical Parkinsonian syndromes (eg, progressive supranuclear palsy, multiple system atrophy). ~~(Part B also)~~	

Section Number and Title	Original Text:	Changed To:	Rationale:
	9. Subject has clinically significant abnormal physical examination OR 12-lead ECG at the screening or admission visits. NOTE: QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study. ECG may be repeated once if initial values obtained are outside the specified limits. (Part B also) 10. Subject has a history, presence and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies 1 and 2. 11. Subject has exposure to another investigational medication or device within 30 days prior to Part A Day 1. 12. Subject has donated one or more units of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing (1 unit = 450 mL). (Part B also) 13. Subject is unwilling or unable to comply with study procedures. (Part B also) 14. Subjects has used any known strong inhibitors and/or inducers of cytochrome P450 (CYP)3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products	~~8~~**9**. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.~~ (Part B also)~~ ~~9~~**10**.Subject has clinically significant abnormal physical examination OR 12-lead ECG at the screening or admission visits. NOTE: QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study. ECG may be repeated once if initial values obtained are outside the specified limits. ~~(Part B also)~~ 1~~0~~**1**.Subject has a history, presence and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies 1 and 2. 1~~1~~**2**.Subject has exposure to another investigational medication or device within 30 days prior to~~ Part A~~ Day 1. 1~~2~~**3**.Subject has donated one or more units of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing (1 unit = 450 mL). ~~(Part B also)~~ 1~~3~~**4**.Subject is unwilling or unable to comply with study procedures. ~~(Part B also)~~	

Section Number and Title	Original Text:	Changed To:	Rationale:
	containing these within 30 days prior to receiving the first dose of study drug. (Part B also)	1~~4~~**5**.Subjects has used any known strong inhibitors and/or inducers of cytochrome P450 (CYP)3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug. ~~(Part B also)~~	
2. Synopsis, Investigational product, dosage and mode of administration	Investigational product, dosage and mode of administration: SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dose.	Investigational product, dosage and mode of administration: **Part A:** SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dose. **Part B: SAGE-217 Capsules are available as hard gelatin capsules containing a white to off-white powder. In addition to SAGE-217 Drug Substance, the SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients. For Part B, capsules will be available in 5-mg, 10-mg and 20-mg dose strengths. Subjects will be administered two capsules per dose.**	Change made to accommodate the availability of a capsule formulation for Part B.
2. Synopsis, Duration of treatment	Duration of treatment: 7 days in Part A; 8 days in Part B	Duration of treatment: ~~7 days in Part A; 8 days in Part B~~**Part A and Part B:**	Changes made due to update in study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
	Part A: Screening duration: up to 28 days; Treatment Period: 7 days (SAGE-217 dosing for 4 days); Follow-up: 7 days Planned participation per subject: approximately 42 days during Part A. Part B: Screening duration: up to 14 days; Treatment Period: 8 days; Follow-up: 14 days Planned participation per subject: approximately 36 days during Part B.	~~Part A:~~ Screening ~~d~~**D**uration: up to 28 days; Treatment Period: 7 days ~~(SAGE-217 dosing for 4 days)~~; Follow-up: 7 days Planned ~~participation~~ **Study Duration** per ~~s~~**S**ubject: approximately 42 days ~~during Part A~~. ~~Part B:~~ ~~Screening duration: up to 14 days; Treatment Period: 8 days; Follow-up: 14 days~~ ~~Planned participation per subject: approximately 36 days during Part B.~~	
2. Synopsis, Reference therapy, dosage and mode of administration	In part B, placebo will be taste-matched to SAGE-217 Oral Solution.	~~In part B, placebo will be taste-matched to SAGE-217 Oral Solution.~~**Not applicable; Part A and Part B are open-label with all subjects receiving SAGE-217.**	Changes made due to update in study design for Part B.
2. Synopsis, Criteria for evaluation	Safety and tolerability: Safety and tolerability of study drug will be evaluated by vital signs, clinical laboratory measures, ECGs, physical examinations, concomitant medication usage, C-SSRS, and adverse event reporting. Sleepiness/sedation will be assessed by the SSS and MOAA/S. Efficacy: Improvement in PD motor symptoms and overall symptoms will be assessed by changes in the MDS UPDRS Part III score and MDS-UPDRS Parts I-IV total score at various time points.	Safety and tolerability: Safety and tolerability of study drug will be evaluated by vital signs, clinical laboratory measures, ECGs, physical examinations, concomitant medication usage, C-SSRS, and adverse event reporting. Sleepiness/sedation will be assessed by the SSS ~~and MOAA/S~~**in Part A only**. Efficacy: **Part A:** Improvement in PD motor symptoms and overall symptoms will be assessed by changes in the MDS UPDRS Part III score and MDS-UPDRS Parts I-IV	Changes made due to update in study objectives and endpoints for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
		total score at various time points. **Part B:** • **Improvement in PD tremor as assessed by changes in the 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).** • **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.**	
2. Synopsis, Pharmacokinetics	Plasma will be collected to assay for concentrations of SAGE-217 and possibly SAGE-217 metabolites. The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), the distributional half-life and terminal half-life ($t_{1/2}$), and steady-state drug concentration in the plasma (C_{ss}).	Plasma will be collected to assay for concentrations of SAGE-217 and possibly SAGE-217 metabolites **in Part A and Part B**. **Part A:** The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), the distributional half-life and terminal half-life ($t_{1/2}$), and steady-state drug concentration in the plasma (C_{ss}).	Changes made to distinguish PK objectives for Part A and Part B

Section Number and Title	Original Text:	Changed To:	Rationale:
		Part B: Area under the curve (AUC), C_{max}, and trough concentration (C_{0h}) at steady-state will be estimated for each individual using the most recent applicable Population PK model.	
2. Synopsis, Statistical methods	Study Populations The safety population, defined as all subjects who are administered study drug, will be used to provide descriptive summaries of safety. The efficacy population, defined as all subjects in the safety population who receive at least one dose of study drug and have at least one postdose MDS-UPDRS evaluation, will be used to analyze efficacy data. The PK population will consist of all subjects in the safety population with sufficient plasma concentrations for PK evaluations and will be used to summarize PK data. Separate populations will be defined for each part of the study. General Considerations Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical	**Sample Size Calculation** **Approximately 18 subjects will be enrolled in Part A. Up to 15 new 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). The sample size for Part A and Part B was selected based on clinical and not statistical considerations.** Study Populations The safety population, defined as all subjects who are administered **at least one dose of** study drug, will be used to provide descriptive summaries of safety. The efficacy population, defined as all subjects in the safety population who receive at least one dose of study drug and have at least one postdose MDS-UPDRS evaluation, will be used to analyze efficacy data. The PK population will consist of all subjects in the safety population **with at least one plasma sample** with sufficient plasma concentrations for PK evaluations and will be used to summarize PK data.	Changes made due to update in study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
	endpoints, descriptive summaries will include counts and percentages. Safety Analysis Adverse events will be coded using Medical Dictionary for Regulatory Activities™ (MedDRA). The overall incidence of adverse events will be displayed by System Organ Class (SOC), preferred term, dose group, and cohort. Incidence of adverse events will also be presented by maximum severity and relationship to study drug. Vital signs, clinical laboratory measures, ECG, and C-SSRS data will be summarized by dose group and cohort, where applicable. Out-of-range safety endpoints may be categorized as low or high, where applicable. Efficacy Analysis Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data. An interim analysis of 10 subjects completing Part A is planned to inform Part B study conduct. Pharmacokinetic Analysis Pharmacokinetic parameters will be summarized using appropriate descriptive statistics and listed by subject.	Separate populations will be defined for each part of the study. General Considerations Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages. Safety Analysis Adverse events will be coded using Medical Dictionary for Regulatory Activities™ (MedDRA). The overall incidence of adverse events will be displayed by System Organ Class (SOC), preferred term, dose group, and ~~cohort~~**total**. Incidence of adverse events will also be presented by maximum severity and relationship to study drug. Vital signs, clinical laboratory measures, ECG, and C-SSRS data will be summarized by dose group and cohort, where applicable. Out-of-range safety endpoints may be categorized as low or high, where applicable. **Subject listings will be provided for all safety data.** Efficacy Analysis Efficacy data will be summarized using appropriate descriptive statistics and other data presentation	

Section Number and Title	Original Text:	Changed To:	Rationale:
		methods where applicable; subject listings will be provided for all efficacy data. An interim analysis of 10 subjects completing Part A is planned to inform Part B study conduct. **No formal interim analysis for Part B subjects is planned.** <u>Pharmacokinetic Analysis</u> **Drug concentrations and p~~P~~**harmacokinetic parameters will be summarized using appropriate descriptive statistics and listed by subject.	
2. Synopsis, Table 3		Removed original table with randomized, placebo-controlled design and replaced with open-label design	

Section Number and Title	Original Text:	Changed To:	Rationale:
5.2 SAGE-217 (previously 5.2 SAGE-217 Oral Solution)	5.2. SAGE-217 Oral Solution SAGE-217 is a positive allosteric modulator of the GABAA receptor and thus is expected to be of benefit for the treatment of ET. Unlike benzodiazepines that are selective for the γ-subunit-containing subset of GABAA receptors (Pritchett 1989, Esmaeili 2009), SAGE-217 and other neuroactive steroids, which bind to the ubiquitous α-subunit, have a wider range of activity (Belelli 2002). SAGE-217 Oral Solution 6 mg/mL (40% w/w aqueous hydroxypropyl-β-cyclodextrin [HPβCD] with 0.025 mg/mL sucralose) is a nonviscous, clear solution.	5.2. SAGE-217 ~~Oral Solution~~ SAGE-217 is a positive allosteric modulator of the GABAA receptor and thus is expected to be of benefit for the treatment of ET. Unlike benzodiazepines that are selective for the γ-subunit-containing subset of GABAA receptors (Pritchett 1989, Esmaeili 2009), SAGE-217 and other neuroactive steroids, which bind to the ubiquitous α-subunit, have a wider range of activity (Belelli 2002). **Two dosage forms of SAGE-217 for oral administration will be used in this study (SAGE-217 Oral Solution and SAGE-217 Capsules).** SAGE-217 Oral Solution 6 mg/mL (40% w/w aqueous hydroxypropyl-β-cyclodextrin [HPβCD] with 0.025 mg/mL sucralose) is a nonviscous, clear solution. **SAGE-217 Capsules are available as hard gelatin capsules containing a white to off-white powder. In addition to the specified amount of SAGE-217 Drug Substance, active, SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients.**	Change made to accommodate the availability of a capsule formulation
5.3.2 Clinical Experience	To date, two clinical studies employing SAGE-217 Oral Solution are clinically complete and final clinical study reports are pending. Discussions of pharmacokinetic (PK) data are limited to the single-	To date, two clinical studies employing SAGE-217 Oral Solution are clinically complete and final clinical study reports are pending. Discussions of pharmacokinetic (PK) data are limited to the single-	Change made to accommodate the availability of a capsule formulation

Section Number and Title	Original Text:	Changed To:	Rationale:
	ascending dose, food effect, and essential tremor cohorts from Study 217-CLP-101 and the multiple-ascending dose and drug-drug interaction cohorts from Study 217-CLP-102. Discussions of safety data are limited to the single-ascending dose cohorts in Study 217-CLP-101 and the multiple-ascending dose cohorts in Study 217-CLP-102. Study 217-CLP-101 was a first-in-human, four-part study that assessed the effects of a single dose of SAGE 217. The study was a double-blind, placebo-controlled, single-ascending dose design in healthy adult volunteers, with the objective of identifying the maximum tolerated dose (MTD) and PK profiles of SAGE-217 Oral Solution. Subjects in each of the single-ascending dose cohorts received a single dose of study drug, either SAGE-217 (six subjects) or placebo (two subjects), with SAGE-217 doses of 0.25 mg, 0.75 mg, 2 mg, 5.5 mg, 11 mg, 22 mg, 44 mg, 55 mg, and 66 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the Safety Review Committee (SRC) and agreement reached that it was safe to increase the dose. The MTD was determined to be 55 mg. Two cohorts, 6 subjects each received SAGE-217 Oral Solution in an open-label manner (one cohort received 50% of the MTD [22 mg] to study the food effects and the other cohort received the MTD [55 mg] to study the effects on subjects with essential tremor). SAGE-217 Oral Solution was orally bioavailable, demonstrated dose-linear PK from the	ascending dose, food effect, and essential tremor cohorts from Study 217-CLP-101 and the multiple-ascending dose and drug-drug interaction cohorts from Study 217-CLP-102. Discussions of safety data are limited to the single-ascending dose cohorts in Study 217-CLP-101 and the multiple-ascending dose cohorts in Study 217-CLP-102. **In addition, one clinical study of the safety, tolerability, PK, and relative bioavailability SAGE-217 Capsules is clinically complete and the final study report is pending. The results of this study (217-CLP-103) are briefly described below.** Study 217-CLP-101 was a first-in-human, four-part study that assessed the effects of a single dose of SAGE 217 **Oral Solution**. The study was a double-blind, placebo-controlled, single-ascending dose design in healthy adult volunteers, with the objective of identifying the maximum tolerated dose (MTD) and PK profiles of SAGE-217 Oral Solution. Subjects in each of the single-ascending dose cohorts received a single dose of study drug, either SAGE-217 **Oral Solution** (six subjects) or placebo (two subjects), with SAGE-217 **Oral Solution** doses of 0.25 mg, 0.75 mg, 2 mg, 5.5 mg, 11 mg, 22 mg, 44 mg, 55 mg, and 66 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the Safety Review Committee (SRC) and agreement reached that it was safe to increase the dose. The MTD was determined to be 55 mg. Two cohorts, 6 subjects each received SAGE-217 Oral	

Section Number and Title	Original Text:	Changed To:	Rationale:
	lowest (0.25 mg) through the highest (66 mg) dose, and supported once daily oral dosing with food. In addition, the pharmacodynamic effects of the SAGE-217 Oral Solution MTD were assessed in placebo-controlled, blinded, crossover electroencephalogram cohorts of 8 subjects each; one cohort received 50% of the MTD (22 mg) and the other received the MTD (55 mg). Study 217-CLP-102 was a two-part study that assessed the effects of multiple-ascending doses of SAGE 217 Oral Solution. The study was a double-blind, placebo-controlled, multiple-ascending dose study in healthy adult volunteers. Subjects in each of the multiple-ascending dose cohorts received study drug, either SAGE-217 (nine subjects) or placebo (three subjects), once daily for 7 days, with SAGE-217 Oral Solution doses of 15 mg, 30 mg, and 35 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the SRC and agreement reached that it was safe to increase the dose. The MTD was determined to be 30 mg. It was observed that subjects receiving the drug in the evening did better in terms of tolerability compared to when they received the drug in the morning. A fourth cohort of 12 subjects received 30 mg of SAGE-217 Oral Solution in an open-label manner to study drug-drug interactions. SAGE-217 Oral Solution is not likely to induce the metabolism of CYP2B6 or CYP3A4 substrates. SAGE-217 Oral Solution was orally	Solution in an open-label manner (one cohort received 50% of the MTD [22 mg] to study the food effects and the other cohort received the MTD [55 mg] to study the effects on subjects with essential tremor). SAGE-217 Oral Solution was orally bioavailable, demonstrated dose-linear PK from the lowest (0.25 mg) through the highest (66 mg) dose, and supported once daily oral dosing with food. In addition, the pharmacodynamic effects of the SAGE-217 Oral Solution MTD were assessed in placebo-controlled, blinded, crossover electroencephalogram cohorts of 8 subjects each; one cohort received 50% of the MTD (22 mg) and the other received the MTD (55 mg). Study 217-CLP-102 was a two-part study that assessed the effects of multiple-ascending doses of SAGE 217 Oral Solution. The study was a double-blind, placebo-controlled, multiple-ascending dose study in healthy adult volunteers. Subjects in each of the multiple-ascending dose cohorts received study drug, either SAGE-217 **Oral Solution** (nine subjects) or placebo (three subjects), once daily for 7 days, with SAGE-217 Oral Solution doses of 15 mg, 30 mg, and 35 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the SRC and agreement reached that it was safe to increase the dose. The MTD was determined to be 30 mg. It was observed that subjects receiving the drug in the evening did better in terms of tolerability compared to when they	

Section Number and Title	Original Text:	Changed To:	Rationale:
	bioavailable and suitable for once daily oral dosing at night time with food. SAGE-217 Oral Solution was generally well tolerated. In both Phase 1 studies (217-CLP-101 and 217-CLP-102), doses were escalated until the stopping criteria were met. Most adverse events were reported as mild or moderate in intensity, and there were no serious adverse events reported in either study. In addition, none of the observed adverse events resulted in discontinuation of the study drug. At doses planned for further study, the observed sedation was mild, transient, and associated with daily peak exposure. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, dizziness, euphoric mood, fatigue, tremor, and muscle twitching, reported most frequently in the highest dose group (66 mg). Some changes in mean blood pressure and heart rate were observed after single doses of 44 mg and greater. After multiple doses of 30 mg (morning [AM] or evening [PM]) or 35 mg (AM) over 7 days, there was no evidence of changes in mean vital sign measures even though Day 7 plasma concentrations approximated that of the highest single dose in the single-ascending dose study. Subjects seemed to tolerate SAGE-217 better when given as night time dosing. Neuroactive steroids are a class of endogenous and synthetic positive allosteric modulators that target	received the drug in the morning. A fourth cohort of 12 subjects received 30 mg of SAGE-217 Oral Solution in an open-label manner to study drug-drug interactions. SAGE-217 Oral Solution is not likely to induce the metabolism of CYP2B6 or CYP3A4 substrates. SAGE-217 Oral Solution was orally bioavailable and suitable for once daily oral dosing at night time with food. SAGE-217 Oral Solution was generally well tolerated. In both Phase 1 studies (217-CLP-101 and 217-CLP-102), doses were escalated until the stopping criteria were met. Most adverse events were reported as mild or moderate in intensity, and there were no serious adverse events reported in either study. In addition, none of the observed adverse events resulted in discontinuation of the study drug. At doses planned for further study, the observed sedation was mild, transient, and associated with daily peak exposure. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, dizziness, euphoric mood, fatigue, tremor, and muscle twitching, reported most frequently in the highest dose group (66 mg). Some changes in mean blood pressure and heart rate were observed after single doses of 44 mg and greater. After multiple doses of 30 mg (morning [AM] or evening [PM]) or 35 mg (AM) over 7 days, there was no evidence of changes in mean vital sign measures even though Day 7 plasma concentrations approximated that of the highest single dose in the	

Section Number and Title	Original Text:	Changed To:	Rationale:
	both synaptic and extra-synaptic GABAA receptors (Belelli 2002 and confirmed in the Sponsor's in vitro studies). This diverse activity profile suggests that neuroactive steroid GABAA receptor-positive allosteric modulators could exhibit robust activity against essential tremor. Administration of SAGE-547 injection, a proprietary formulation of the endogenous neuroactive steroid, resulted in significant reductions in upper limb kinetic tremor scores compared to placebo in a Phase 2 proof-of-principle study (IND 122,280). Based on these results with SAGE-547, the study design for single-ascending dose study 217-CLP-101 included a cohort of subjects with essential tremor (N=6) who received SAGE-217 Oral Solution (55 mg) in an open-label manner. Data from this cohort indicate that single doses of SAGE-217 Oral Solution resulted in a reduction in the tremor symptoms, suggesting that SAGE-217 might be effective in treating PD. There are no clinical efficacy data of SAGE-217 Oral Solution in PD, since the present study is the first study in this indication.	single-ascending dose study. Subjects seemed to tolerate SAGE-217 Oral Solution better when given as night time dosing. **The safety, tolerability, PK, and relative bioavailability of the SAGE-217 Capsules were assessed in a Phase 1 randomized, open-label, cross-over study (Study 217-CLP-103). In the fasted state, SAGE-217 Capsules demonstrated reduced exposure in terms of maximum (peak) plasma concentration (C_{max}) and area under the curve from zero to the time of the last quantifiable concentration (AUC_{last}) compared to SAGE-217 Oral Solution. SAGE-217 Capsules administered in the fed state (with standard and high-fat meal) showed increased exposure compared to the fasted state and approximately equivalent exposure in terms of geometric mean AUC_{last} compared to SAGE-217 Oral Solution; however, the C_{max} for SAGE-217 Capsules was reduced by approximately 50% when compared with SAGE-217 Oral Solution. Based on these study results, exposures with SAGE-217 Capsules are anticipated to be equal to or less than exposures observed at the same dose with SAGE-217 Oral Solution.** Neuroactive steroids are a class of endogenous and synthetic positive allosteric modulators that target both synaptic and extra-synaptic GABAA receptors (Belelli 2002 and confirmed in the Sponsor's in vitro	

Section Number and Title	Original Text:	Changed To:	Rationale:
		studies). This diverse activity profile suggests that neuroactive steroid GABAA receptor-positive allosteric modulators could exhibit robust activity against essential tremor. Administration of SAGE-547 injection, a proprietary formulation of the endogenous neuroactive steroid, resulted in significant reductions in upper limb kinetic tremor scores compared to placebo in a Phase 2 proof-of-principle study (IND 122,280). Based on these results with SAGE-547, the study design for single-ascending dose study 217-CLP-101 included a cohort of subjects with essential tremor (N=6) who received SAGE-217 Oral Solution (55 mg) in an open-label manner. Data from this cohort indicate that single doses of SAGE-217 Oral Solution resulted in a reduction in the tremor symptoms, suggesting that SAGE-217 might be effective in treating PD. There are no clinical efficacy data of SAGE-217 Oral Solution **or Capsules** in PD, since the present study is the first study in this indication.	
5.4. Potential Risks and Benefits	Protocol 217-PRK-201 is the first clinical study evaluating the efficacy of SAGE-217 Oral Solution in PD. Thus, the potential benefits in this population are unknown, although the risks are likely to be similar to those mentioned in the Investigator's Brochure. GABA compounds that cross the blood-brain barrier or increase GABA activity alleviate muscle stiffness caused by a lack of GABAergic tone (Winkler 1999), validating this receptor as a	Protocol 217-PRK-201 is the first clinical study evaluating the efficacy of SAGE-217 ~~Oral Solution~~ in PD. Thus, the potential benefits in this population are unknown, although the risks are likely to be similar to those mentioned in the Investigator's Brochure. GABA compounds that cross the blood-brain barrier or increase GABA activity alleviate muscle stiffness caused by a lack of GABAergic tone (Winkler 1999), validating this receptor as a therapeutic target. Given	a) Change made to accommodate the availability of a capsule formulation; b) Changes made due to update in study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
	therapeutic target. Given the promising clinical data with another neuroactive steroid (SAGE-547) in conjunction with the shared broad receptor selectivity profile, oral bioavailability, long half-life, preclinical evidence of anxiolytic activity, and safety data of SAGE-217, it is possible that patients may have a clinical benefit at the exposures selected for this study. In view of the few risks associated with administration of SAGE-217 Oral Solution that have been identified to date, an intra-patient dose-reduction design has been chosen to permit reduction in dose based on tolerability (adverse events), specifically sedation, versus treatment effect. Each subject will start with an initial dose of 30 mg; subjects unable to tolerate 30 mg will receive 20 mg; subjects unable to tolerate 20 mg will receive 10 mg. The tolerated dose for each subject will be the dose taken on Day 7. Subjects who tolerate at least the 10 mg dose on Day 7 will be eligible to enroll in Part B. Given the high medical need and potential for benefit in PD, there is a favorable benefit-risk evaluation to investigate SAGE-217 Oral Solution in PD. In conclusion, selection criteria for the proposed study take into account the potential safety risks. Continuous safety monitoring, and the implementation of a formal dose-reduction and study drug discontinuation scheme also have the potential to mitigate risk. From a benefit/risk perspective, the appropriate measures are being	the promising clinical data with another neuroactive steroid (SAGE-547) in conjunction with the shared broad receptor selectivity profile, oral bioavailability, long half-life, preclinical evidence of anxiolytic activity, and safety data of SAGE-217, it is possible that patients may have a clinical benefit at the exposures selected for this study. **In the 217-CLP-103 study, SAGE-217 Capsules were found to be generally well-tolerated with no serious AEs reported during the treatment and follow-up periods. The most frequent AE observed was sedation that was mild, transient, and occurred within 1 to 4 hours following dosing and generally dissipated by 8 hours. The clinical portion of this study has recently completed; the final report is in progress.** In view of the few risks associated with administration of SAGE-217 ~~Oral Solution~~ that have been identified to date, an intra-patient dose-reduction design**s** ha~~s~~**ve** been chosen **for Part A and Part B** to permit reduction in dose based on tolerability (adverse events), specifically sedation, versus treatment effect. **In Part A**, ~~E~~**e**ach subject will start with an initial dose of **SAGE-217 Oral Solution,** 30 mg; subjects unable to tolerate 30 mg will receive 20 mg; subjects unable to tolerate 20 mg will receive 10 mg. **In Part B, each subject will receive SAGE-217 in the evening (PM) starting with an initial dose of SAGE-217 Capsules, 20 mg**	

Section Number and Title	Original Text:	Changed To:	Rationale:
	taken in order to ensure the safety of the subjects who will be enrolled.	**for two days; subjects able to tolerate 20 mg will receive 30 mg. If the subject is unable to tolerate 30 mg, the subject will receive 20 mg and continue for the remainder of the dosing period. Subjects who cannot tolerate the 20-mg dose at any time during Part B will be discontinued and replaced.** The tolerated dose for each subject **in Part A and Part B** will be the dose taken on Day 7. ~~Subjects who tolerate at least the 10 mg dose on Day 7 will be eligible to enroll in Part B.~~ Given the high medical need and potential for benefit in PD, there is a favorable benefit-risk evaluation to investigate SAGE-217 ~~Oral Solution~~ in PD. In conclusion, selection criteria for the proposed study take into account the potential safety risks. Continuous safety monitoring, and the implementation of a formal dose-reduction and study drug discontinuation scheme also have the potential to mitigate risk. From a benefit/risk perspective, the appropriate measures are being taken in order to ensure the safety of the subjects who will be enrolled.	
6.1. Primary Objective	The primary objective of this study is to evaluate the safety and tolerability of SAGE-217 Oral Solution.	The primary objective of ~~this study is to evaluate the safety and tolerability of SAGE-217 Oral Solution.~~ **Part A is** • **To evaluate the safety and tolerability of SAGE-217 Oral Solution.** **The primary objective of Part B is:**	Changes made due to update in study design for Part B and availability of a capsule formulation.

Section Number and Title	Original Text:	Changed To:	Rationale:
		• **To evaluate the effect of SAGE-217 Capsules as an adjunct to antiparkinsonian agent(s) on the severity of PD tremor symptoms.**	
6.2. Secondary Objectives	The secondary objectives of the study 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. • To compare the effect of SAGE-217 Oral Solution in combination with immediate-release oral Levodopa/Carbidopa to Levodopa/Carbidopa alone.	The secondary objectives of ~~the study~~ **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. • ~~To compare the effect of SAGE-217 Oral Solution in combination with immediate-release oral Levodopa/Carbidopa to Levodopa/Carbidopa alone.~~ **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.**	a) Changes made to divide the study objectives of Part A and Part B and make efficacy the primary objective for Part B; b) objectives added due to update of study design for Part B (randomized to open-label) and availability of SAGE-217 Capsule; c) added Pharmacokinetic objectives that were inadvertently missing from previous version
New section		**6.3. Pharmacokinetic Objectives** **The PK objective of Part A is:** • **To assess the PK profile of SAGE-217 Oral Solution in plasma samples.**	Section was inadvertently missing from previous version

Section Number and Title	Original Text:	Changed To:	Rationale:
		The PK objective of Part B is: • **To assess the PK profile of SAGE-217 Capsules utilizing a population PK approach.**	
6.3.1. Exploratory Endpoints	6.3.1 Primary Endpoints • Frequency and severity of adverse events and changes 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.	6.~~3~~**4**.1 Primary Endpoints **Part A:** • Frequency and severity of adverse events and changes 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~~. **In addition, sleepiness/sedation as assessed by Stanford Sleepiness Scale (SSS) score.** **Part B:** • **Improvement in PD tremor as assessed by changes in the 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).**	a) Changes made due to division of study objectives between Part A and Part B; b) changes made due to update in study design for Part B
6.3.2. Secondary Endpoints	6.3.2 Secondary Endpoints 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) score.	6.~~3~~**4**.2 Secondary Endpoints 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:	Changes made due to update in study objectives and design for Part B

Section Number and Title	Original Text:	Changed To:	Rationale:
	Part B: • Improvement in PD motor symptoms as assessed by changes in the MDS-UPDRS – Part III score. • Improvement in PD overall symptoms as assessed by changes in the MDS-UPDRS – Parts I-IV total score. • Sleepiness/sedation as assessed by the Stanford Sleepiness Scale (SSS) and Modified Observer's Assessment of Analgesia/Sedation (MOAA/S) scores.	• 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. • **Frequency and severity of adverse events and changes in vital signs, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS).** • ~~Sleepiness/sedation as assessed by the Stanford Sleepiness Scale (SSS) and Modified Observer's Assessment of Analgesia/Sedation (MOAA/S) scores.~~	
New section		**6.4.3 Pharmacokinetic Endpoints** • **Plasma concentrations of SAGE-217, and possibly SAGE-217 metabolites, will be measured, and PK parameters will be derived.**	Section was inadvertently missing from previous version
6.3.3. Exploratory Endpoints	6.3.3. Exploratory Endpoints • [redacted]	6.~~3~~**4**.~~3~~**4**. Exploratory Endpoints • [redacted]	[redacted]

Section Number and Title	Original Text:	Changed To:	Rationale:
[redacted]	[redacted]	[redacted]	[redacted]

Section Number and Title	Original Text:	Changed To:	Rationale:
		[redacted]	
7.1. Overall Study Design	This study is a two-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 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	This study is a two-part, multicenter, Phase 2 study to evaluate the safety, tolerability, PK, and efficacy of SAGE-217 ~~Oral Solution~~**. Part A of the study is an open-label design with morning (AM) dosing of SAGE-217 Oral Solution for 4 days in** 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 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.~~ **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 not eligible to participate in Part B. Subjects will be followed for**	Changes made due to update in study design for Part B and availability of SAGE-217 capsule.

Section Number and Title	Original Text:	Changed To:	Rationale:
	in the AM only 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 morning with food, as outlined in Section 9.1.1. 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). 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 interim analysis.	**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 **of SAGE-217 Oral Solution** (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 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 morning with food, as outlined in Section 9.1.1. 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). 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	

Section Number and Title	Original Text:	Changed To:	Rationale:
	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 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. Subjects randomized to the Levodopa plus placebo arm will receive Levodopa and SAGE 217 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	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 interim analysis.~~ ~~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 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. Subjects randomized to the Levodopa plus placebo arm will receive Levodopa and SAGE 217 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~~	

Section Number and Title	Original Text:	Changed To:	Rationale:
	any time the dose is not tolerated, assessed by occurrence of a severe adverse event 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 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 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. The study designs of Part A and Part B are displayed in Figure 1 and Figure 2, respectively. Assessments will be performed periodically during the study as outlined in the Schedule of Events for Part A and Part B (Table 2 and Table 3, respectively).	~~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 adverse event 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 wi~~ll receive a 10 mg dose on subsequent days). The dose 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 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.~~ **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**	

Section Number and Title	Original Text:	Changed To:	Rationale:
		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 (e.g., 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 (i.e., those who do not experience a severe adverse event 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 adverse event 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 outline in Section 9.1.2. For antiparkinsonian agents, administration with or**	

Section Number and Title	Original Text:	Changed To:	Rationale:
		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.** The study designs of Part A and Part B are displayed in Figure 1 and Figure 2, respectively. Assessments will be performed periodically during the study as outlined in the Schedule of Events for Part A and Part B (Table 2 and Table 3, respectively).	
7.3. Treatment Assignment	SAGE-217 will be administered in the morning with food in Parts A and B. Food intake will be standardized as specified by the Sponsor. If subjects are taking Levodopa as opposed to Carbidopa-Levodopa, administration with or without food will be determined by the Investigator. Part A of the study is open-label. Part B of the study is randomized, placebo-controlled, two-sequence crossover. Subjects will be randomly assigned in a 1:1 manner to receive open-label Levodopa plus blinded SAGE 217 Oral Solution or placebo for 4 days (Days 1 to 4, Period 1 of crossover). Subjects, clinicians, and the study team will be blinded to treatment allocation. The pharmacist, who will prepare the oral solutions according to the randomization schedule, will be unblinded. For the remaining 4 days of Part B (Days 5 to 8, Period 2 of crossover), all subjects will discontinue Levodopa	SAGE-217 will be administered ~~in the morning~~ with food in Parts A and B. Food intake will be standardized as specified by the Sponsor. If subjects are taking ~~Levodopa as opposed to Carbidopa Levodopa~~**antiparkinsonian agent(s)**, administration with or without food will be determined by the Investigator. Part**s** A **and B** of the study ~~is~~**are** open-label. ~~Part B of the study is randomized, placebo-controlled, two sequence crossover. Subjects will be randomly assigned in a 1:1 manner to receive open label Levodopa plus blinded SAGE 217 Oral Solution or placebo for 4 days (Days 1 to 4, Period 1 of crossover). Subjects, clinicians, and the study team will be blinded to treatment allocation. The pharmacist, who will prepare the oral solutions according to the randomization schedule, will be unblinded. For the remaining 4 days of Part B (Days~~	Changes made due to update in study design for Part B

Section Number and Title	Original Text:	Changed To:	Rationale:
	and will receive their individually established tolerated dose of SAGE-217 Oral Solution from Part A in an open-label manner. Dose reductions for lack of tolerability will be allowed during both parts of the study (Section 7.4).	~~5 to 8, Period 2 of crossover), all subjects will discontinue Levodopa and will receive their individually established tolerated dose of SAGE 217 Oral Solution from Part A in an open label manner.~~ Dose reductions for lack of tolerability will be allowed during both parts of the study (Section 7.4).	
7.4. Dose Adjustment Criteria	Dose reductions of SAGE-217 for lack of tolerability will be allowed during both parts of the study. If at any time the dose is not tolerated in Part A, as determined by the Investigator, the dose on the next day will be reduced to the next lowest dose (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 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	Dose reductions of SAGE-217 for lack of tolerability will be allowed during both parts of the study. If at any time the dose is not tolerated in Part A, as determined by the Investigator, the dose on the next day will be reduced to the next lowest dose (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 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~~**In Part B, subjects tolerating the initial 20-mg dose on Days 1 and 2 will receive a 30-mg dose on Day 3 and continue for the remainder of the dosing period. If on Day 3 or any time thereafter, the 30-mg dose is not tolerated, the dose on the next day must be reduced to 20 mg and continued for the remainder of the dosing period.**	Changes made due to update in study design for Part B

Section Number and Title	**Original Text:**	**Changed To:**	**Rationale:**
Figure 1 footnote	NOTE: In order to qualify for Part B of the study, a subject must tolerate a dose of at least 10 mg of SAGE-217 Oral Solution in Part A.	removed	Removed due to update in study design for Part B
Figure 2		updated	Updated figure to reflect new study design for Part B
Section 8. Selection and Withdrawal of Subjects	It is anticipated that up to 18 subjects will be enrolled in Part A at up to 4 study centers. All of the following inclusion and exclusion criteria will be applied during screening for Part A, with some of the criteria applied during screening for Part B, as indicated.	~~It is anticipated that up to 18 subjects will be enrolled in Part A at up to 4 study centers. All of the following inclusion and exclusion criteria will be applied during screening for Part A, with some of the criteria applied during screening for Part B, as indicated.~~	Not applicable with updated study design for Part B.
8.3. Entrance Criteria for Part B		Removed section	Not applicable with updated study design for Part B.
8.4. (previously 8.3.) Subject Withdrawal Criteria	Subjects may be withdrawn from the study if there is concern for the subject's safety or it is determined that the subject is no longer a qualified participant. Any subject who is withdrawn from the study for any reason is to have the final visit assessments performed.	Subjects may be withdrawn from the study if there is concern for the subject's safety or it is determined that the subject is no longer a qualified participant. **Subjects who cannot tolerate the 10-mg dose at any time during Part A or the 20-mg dose at any time during Part B will be withdrawn.** Any subject who is withdrawn from the study for any reason is to have the final visit assessments performed.	Change made due to update in study design for Part B.

Section Number and Title	**Original Text:**	**Changed To:**	**Rationale:**
9.1. Description of Study Drug	9.1. Description of Study Drug For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol.	9.1. Description of Study Drug **Treatment** For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol. **All doses of SAGE-217 (Oral Solution or Capsule) will be administered with food.**	Change made due to availability of SAGE-217 Capsule
9.1.1. Part A	Subjects participating in Part A of the study will take study drug (SAGE-217) in an open-label manner. 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 the following 3 days (Days 1 to 3). On the morning of Day 4, subjects will stop their immediate-release oral Levodopa and take SAGE-217 for 4 days (Days 4 to 7) in the AM with food. On Day 4, subjects will receive a 30 mg dose of SAGE-217. Subjects not tolerating 30 mg will receive 20 mg the next day, and subjects not tolerating 20 mg will receive 10 mg the next day. The dose received on Day 7 will be defined as the tolerated dose for that subject, with this dose to be used as the starting dose for Part B for that subject. Subjects not tolerating 10 mg will not be able to continue in the study and may be replaced. Levodopa treatment will be resumed on Day 8 and continue through Day 14.	Subjects participating in Part A of the study will take ~~study drug (~~SAGE-217~~)~~ **Oral Solution** in an open-label manner. 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 the following 3 days (Days 1 to 3). On the morning of Day 4, subjects will stop their immediate-release oral Levodopa and take SAGE-217 for 4 days (Days 4 to 7) in the AM with food. On Day 4, subjects will receive a 30 mg dose of SAGE-217. Subjects not tolerating 30 mg will receive 20 mg the next day, and subjects not tolerating 20 mg will receive 10 mg the next day. The dose received on Day 7 will be defined as the tolerated dose for that subject~~, with this dose to be used as the starting dose for Part B for that subject~~. Subjects not tolerating 10 mg will not be able to continue in the study and may be replaced. Levodopa treatment will be resumed on Day 8 and continue through Day 14.	Changes made to distinguish between SAGE-217 Oral Solution and Capsule, due to availability and use of Capsule in Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
9.1.1. Part B	In order to qualify for Part B of the study, a subject must tolerate a dose of at least 10 mg of SAGE-217 Oral Solution. On Day 1 of Part B, subjects will be randomized in a 1:1 manner to open-label Levodopa plus blinded SAGE-217 Oral Solution or placebo. • Subjects randomized to the Levodopa plus placebo arm will receive Levodopa plus SAGE-217 placebo oral solution in the AM for the first 4 days (Days 1 to 4). • Subjects randomized to the Levodopa plus SAGE-217 Oral Solution arm will receive this combination in the AM for the first 4 days (Days 1 to 4). Subjects will receive their individually established tolerated dose of SAGE-217 Oral Solution from Part A. • 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.	~~In order to qualify for Part B of the study, a subject must tolerate a dose of at least 10 mg of SAGE-217 Oral Solution. On Day 1 of Part B, subjects will be randomized in a 1:1 manner to open-label Levodopa plus blinded SAGE-217 Oral Solution or placebo.~~ ~~• Subjects randomized to the Levodopa plus placebo arm will receive Levodopa plus SAGE-217 placebo oral solution in the AM for the first 4 days (Days 1 to 4).~~ ~~• Subjects randomized to the Levodopa plus SAGE-217 Oral Solution arm will receive this combination in the AM for the first 4 days (Days 1 to 4). Subjects will receive their individually established tolerated dose of SAGE-217 Oral Solution from Part A.~~ ~~• 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.~~ **Subjects participating in Part B of the study will take SAGE-217 Capsules in an open-label manner. Subjects on a stable dose of antiparkinsonian agent(s) will continue taking them for the duration**	Changes made due to update in study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
		of the study. All subjects will receive SAGE-217, 20 mg, at 8PM on Days 1 and 2. On Day 3, subjects tolerating the initial dose (i.e., those who do not experience a severe adverse event judged by the Investigator to be related to study drug) will receive a dose increase (SAGE-217, 30 mg), at 8PM, 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 adverse event 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.**	
9.2.2. Prohibited Medications	Subjects who have used any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug are to be excluded from the study; these medications/products are prohibited during the study. The anticholinergic drug classes listed in Appendix 3 and amantadine are not permitted in the 5 days	Subjects who have used any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug are to be excluded from the study; these medications/products are prohibited during the study. The anticholinergic drug classes listed in Appendix 3 ~~and amantadine~~ are not permitted in the 5 days prior to the admission visit (Day -1) of ~~each part of the~~	Changes made to distinguish between Part A and Part B and to reflect update study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
	prior to the admission visit (Day -1) of each part of the study. The list provides non-exhaustive examples of each drug class.	~~study~~**Part A and Part B**. The list provides non-exhaustive examples of each drug class. **Amantadine is not permitted in the 5 days prior to the admission visit of Part A or 9 days prior to the admission visit of Part B.** **The tremorogenic drugs listed in Appendix 4 are not permitted in the 14 days prior to the admission visit of Part B.**	
9.3. Treatment Compliance	Study drug (SAGE-217 or matched placebo) will be prepared by the site pharmacist.	Study drug (SAGE-217 **Oral Solution** or ~~matched placebo~~**Capsule**) will be prepared by the site pharmacist.	Changes made to reflect change in study design for Part B (no longer placebo-controlled) and accommodate availability of SAGE-217 Capsule.
9.4. Randomization and Blinding	Part A of the study is open-label. In 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 groups: open-label Levodopa plus blinded SAGE 217 Oral Solution or placebo oral solution. Subjects, clinicians, and the study team will be blinded to treatment allocation. The pharmacist, who will prepare the oral solutions according to the randomization schedule, will be unblinded.	**Not applicable;** Part A **and Part B** of the study ~~is~~**are** open-label. ~~In 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 groups: open-label Levodopa plus blinded SAGE 217 Oral Solution or placebo oral solution. Subjects, clinicians, and the study team will be blinded to treatment allocation. The pharmacist, who will~~	Changes made to reflect change in study design for Part B (no longer randomized, placebo-controlled).

Section Number and Title	Original Text:	Changed To:	Rationale:
	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	~~prepare the oral solutions 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~~	

Section Number and Title	Original Text:	Changed To:	Rationale:
	been unblinded, the subject will be terminated from the study.	~~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.~~	
10.1. Study Drug	10.1. Study Drug SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dosages. The 6 mg/mL stock SAGE-217 Oral Solution will be compounded from SAGE-217 Drug Substance Powder in the Bottle and Excipient(s) in the Bottle (manufactured under current Good Manufacturing Practice [GMP] conditions [redacted]) and further admixed at the clinical site in preparation for dosing. Placebo will be matched to SAGE-217 study drug. Detailed instructions for study drug preparation will be provided in the Pharmacy Manual. The Sponsor will not provide Levodopa or Carbidopa-Levodopa during the study; subjects will use their prescribed Levodopa or Carbidopa-Levodopa.	10.1. Study Drug **10.1.1. SAGE-217 Oral Solution** SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dosages. The 6 mg/mL stock SAGE-217 Oral Solution will be compounded from SAGE-217 Drug Substance Powder in the Bottle and Excipient(s) in the Bottle (manufactured under current Good Manufacturing Practice [GMP] conditions [redacted]) and further admixed at the clinical site in preparation for dosing. ~~Placebo will be matched to SAGE-217 study drug.~~ Detailed instructions for study drug preparation will be provided in the Pharmacy Manual. The Sponsor will not provide Levodopa or Carbidopa-Levodopa during the study; subjects will use their prescribed Levodopa or Carbidopa-Levodopa.	a) Change made to accommodate the availability of a capsule formulation; b) Change made to reflect change in study design for Part B (no longer placebo-controlled).

Section Number and Title	Original Text:	Changed To:	Rationale:
10.1.2. SAGE-217 Capsules (new section)		**10.1.2. SAGE-217 Capsule** **SAGE-217 Capsules are available as hard gelatin capsules containing a white to off-white powder. In addition to the specified amount of SAGE-217 Drug Substance, active SAGE-217 Capsules contain croscarmellose sodium, mannitol, silicified microcrystalline cellulose, and sodium stearyl fumarate as excipients. Capsules will be available in 5-mg, 10-mg and 20-mg dose strengths. Subjects will be administered two capsules per dose. Detailed instructions for study drug preparation will be provided in the Pharmacy Manual.**	Change made to accommodate the availability of a capsule formulation
10.2. Study Drug Packaging and Labeling	The composition and pharmaceutical quality of the investigational product will be maintained according to the current GMP and Good Clinical Practice (GCP) guidelines and available for review in the study medication documentation. Study drug will be provided to the site as powder in the bottle and excipient(s) in the bottle units to be compounded in the pharmacy at a volume of 125 mL of a 6 mg/mL stock solution and then further diluted to approximately 40 mL at the identified doses. Study drug labels with all required information and conforming to all applicable Code of Federal Regulations and GMP/GCP guidelines will be prepared by the clinical research organization.	The composition and pharmaceutical quality of the investigational product will be maintained according to the current GMP and Good Clinical Practice (GCP) guidelines and available for review in the study medication documentation. ~~Study drug~~**SAGE-217 Oral Solution** will be provided to the site as powder in the bottle and excipient(s) in the bottle units to be compounded in the pharmacy at a volume of 125 mL of a 6 mg/mL stock solution and then further diluted to approximately 40 mL at the identified doses. **SAGE-217 Capsules will be provided to the site in appropriately labeled bottles.** Study drug labels with all required information and conforming to all applicable Code of	Change made to accommodate the availability of a capsule formulation

Section Number and Title	Original Text:	Changed To:	Rationale:
		Federal Regulations and GMP/GCP guidelines will be prepared by the clinical research organization.	
10.3. Study Drug Storage	Upon receipt of study drug (SAGE-217 Oral Solution and placebo oral solution), the Investigator or designee will inspect the materials and complete and return the acknowledgment of receipt form enclosed with the parcel. A copy of the signed receipt will be kept in the study files. The study drug materials for SAGE-217 Oral Solution and placebo oral solution must be carefully stored at the temperature specified in the Pharmacy Manual (eg, clinical dosing solutions stored at approximately 2 to 8°C for 11 days with 24 hours of room temperature excursions allowed after preparation), safely and separately from other drugs.	Upon receipt of study drug (SAGE-217 ~~Oral Solution and placebo oral solution~~), the Investigator or designee will inspect the materials and complete and return the acknowledgment of receipt form enclosed with the parcel. A copy of the signed receipt will be kept in the study files. The study drug materials for SAGE-217 Oral Solution ~~and placebo oral solution~~ must be carefully stored at the temperature specified in the Pharmacy Manual (eg, clinical dosing solutions stored at approximately 2 to 8°C for 11 days with 24 hours of room temperature excursions allowed after preparation), safely and separately from other drugs. **SAGE-217 Capsules may be stored at room temperature.**	a) Change made to accommodate the availability of a capsule formulation; b) Changes made to reflect change in study design for Part B (no longer placebo-controlled).
10.4. Study Drug Preparation	Each bottle of SAGE-217 Oral Solution 6 mg/mL will be compounded at the clinical pharmacy from components manufactured [redacted] and supplied by the Sponsor per the directions provided in the Pharmacy Manual. The batch formula for a 125 mL solution of the 6 mg/mL stock solution is shown in Table 5. Table 5: Batch Formula for 125 mL of Stock SAGE-217 Oral Solution 6 mg/mL	Each bottle of SAGE-217 Oral Solution 6 mg/mL will be compounded at the clinical pharmacy from components manufactured [redacted] and supplied by the Sponsor per the directions provided in the Pharmacy Manual. The batch formula for a 125 mL solution of the 6 mg/mL stock solution is shown in Table 5. Table 5: Batch Formula for 125 mL of Stock SAGE-217 Oral Solution 6 mg/mL	Change made to accommodate the availability of a capsule formulation

Section Number and Title	Original Text:	Changed To:	Rationale:
	Additional excipients may be utilized in placebo to match the taste of SAGE-217 Oral Solution. They include sucrose octaacetate, tannic acid, and ammonium glycyrrhizate. The quantities may vary depending on the dose of SAGE-217.	~~Additional excipients may be utilized in placebo to match the taste of SAGE-217 Oral Solution. They include sucrose octaacetate, tannic acid, and ammonium glycyrrhizate. The quantities may vary depending on the dose of SAGE-217.~~ **For the capsule formulation, subjects will swallow two capsules per dose with food.**	
10.5. Administration	SAGE-217 Oral Solution or placebo oral solution will be administered in the morning with food. Doses of SAGE-217 and placebo for SAGE-217 will be prepared as an approximate 40 mL oral solution to be swallowed all at once, followed by approximately 200 mL of water that has been used to rinse the dosing bottle. The start time of swallowing the approximately 40 mL oral solution is time zero for all assessments. Subjects may have assistance from the clinic staff when taking the study drug. During Confinement, each subject's antiparkinsonian agents, including Levodopa or Carbidopa-Levodopa, will be administered by site personnel according to the site's standard operating procedures.	SAGE-217 ~~Oral Solution or placebo oral solution~~ will be administered **with food** in the morning ~~with food~~**in Part A and in the evening in Part B**. Doses of SAGE-217 ~~and placebo for SAGE-217~~**Oral Solution** will be prepared as an approximate 40 mL oral solution to be swallowed all at once, followed by approximately 200 mL of water that has been used to rinse the dosing bottle. The start time of swallowing the approximately 40 mL oral solution is time zero for all assessments. Subjects may have assistance from the clinic staff when taking the study drug. During Confinement, each subject's antiparkinsonian agents, including Levodopa or Carbidopa-Levodopa, will be administered by site personnel according to the site's standard operating procedures.	a) Change made to accommodate the availability of a capsule formulation; b) Changes made to reflect change in study design for Part B (no longer placebo-controlled and no longer morning dosing).
10.6. Study Drug Accountability	The study drug provided is for use only as directed in this protocol.	The study drug provided is for use only as directed in this protocol.	Changes made to reflect change in study design for Part

Section Number and Title	Original Text:	Changed To:	Rationale:
	The Investigator or designee must maintain a record of all study drug received, used, and discarded. It must be clear from the records which subject received which dose of active or placebo treatment. The Sponsor will be permitted access to the study supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation. Only unblinded personnel will be able to access the study drug and accountability documentation from first dosing through database hard lock. The Investigator will document all doses of Levodopa or Carbidopa-Levodopa taken by the subject, including rescue doses.	The Investigator or designee must maintain a record of all study drug received, used, and discarded. ~~It must be clear from the records which subject received which dose of active or placebo treatment.~~ The Sponsor will be permitted access to the study supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation. ~~Only unblinded personnel will be able to access the study drug and accountability documentation from first dosing through database hard lock.~~ The Investigator will document all doses of Levodopa or Carbidopa-Levodopa taken by the subject, including rescue doses.	B (no longer placebo-controlled)
10.7. Study Drug Handling and Disposal	The pharmacist or designee for drug accountability is to document the date and time of initial compounding, subsequent admixture of dosing solutions, administration of study drug, and for which subject the study drug was intended (ie, record subject initials and birth date or other unique identifier). At the end of the study, any unused study drug will be retained or returned to the Sponsor for destruction or destroyed locally per the Sponsor's directions; disposition of study drug will be documented.	The pharmacist or designee for drug accountability is to document the date and time of initial compounding **(oral solution only)**, subsequent admixture of dosing solutions **(oral solution only)**, administration of study drug, and for which subject the study drug was intended (ie, record subject initials and birth date or other unique identifier). At the end of the study, any unused study drug will be retained or returned to the Sponsor for destruction or destroyed locally per the Sponsor's directions; disposition of study drug will be documented.	Change made to accommodate the availability of a capsule formulation

Section Number and Title	Original Text:	Changed To:	Rationale:
11. Assessment of Efficacy	Efficacy assessments include evaluation of PD symptoms by the MDS-UPDRS, [redacted] Assessments will be performed periodically during the study as outlined in the Schedule of Events (Table 2 and Table 3, respectively).	Efficacy assessments include evaluation of PD symptoms by the MDS-UPDRS, [redacted]. Assessments will be performed periodically during the study as outlined in the Schedule of Events **for Part A and Part B** (Table 2 and Table 3, respectively).	Clarification for respective table reference
11.1 Movement Disorder Society – Unified Parkinson's Disease Rating Scale	The UPDRS is the most commonly used scale in clinical studies of PD (Ramaker 2002). In 2007, the MDS revised the scale, which was known as the MDS-UPDRS (Goetz 2007), and subsequently demonstrated the validity of the MDS-UPDRS for rating PD (Goetz 2008). The modified UPDRS includes four scales, with various subscales. Each item is rated from 0 (normal) to 4 (severe) (Table 6). 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) Table 6: Rating Scale for the MDS-UPDRS Several questions in Part I and all questions in Part II can be answered by the patient/caregiver and	The UPDRS is the most commonly used scale in clinical studies of PD (Ramaker 2002). In 2007, the MDS revised the scale, which was known as the MDS-UPDRS (Goetz 2007), and subsequently demonstrated the validity of the MDS-UPDRS for rating PD (Goetz 2008). The modified UPDRS includes four scales, with various subscales. Each item is rated from 0 (normal) to 4 (severe) (Table 6). 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) Table 6: Rating Scale for the MDS-UPDRS Several questions in Part I and all questions in Part II can be answered by the patient/caregiver and	a) Changes made to reflect change in study design for Part B; b) added MDS-UPDRS Part II text due to additional endpoint for Part B; c) clarified that all MDS-UPDRS measurements should be taken during the "on" period for Part B and defined "on" period; d) Added reference to appendix containing MDS-UPDRS (reference inadvertently

Section Number and Title	Original Text:	Changed To:	Rationale:
	completed without the Investigator's input. The remaining questions in Part I that deal with complex behaviors, the objective assessments of parkinsonism (Part III), and the questions that deal with motor fluctuations and dyskinesias (Part IV) are completed by Investigator interview. The time required for administering the MDS-UPDRS is estimated to be less than 10 minutes for the interview items of Part I, 15 minutes for Part III, and 5 minutes for Part IV (Goetz 2008). The complete MDS-UPDRS is to be administered in Part A at screening, Admission (Day -1), on Day 8 prior to resuming Levodopa, and on Day 14. The complete MDS-UPDRS is to be administered in Part B at screening, Admission (Day -1), on Day 9 prior to resuming Levodopa; and on Days 15 and 22. In both Parts A and B, the Admission (Day -1) complete MDS-UPDRS is performed only if the time between Screening and Admission is ≥7 days; otherwise, the MDS UPDRS Part III only is performed. Part III of the MDS-UPDRS 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, global spontaneity	completed without the Investigator's input. The remaining questions in Part I that deal with complex behaviors, the objective assessments of parkinsonism (Part III), and the questions that deal with motor fluctuations and dyskinesias (Part IV) are completed by Investigator interview. The time required for administering the MDS-UPDRS is estimated to be less than 10 minutes for the interview items of Part I, 15 minutes for Part III, and 5 minutes for Part IV (Goetz 2008). The complete MDS-UPDRS is to be administered in Part A at screening, Admission (Day -1), on Day 8 prior to resuming Levodopa, and on Day 14. The complete MDS-UPDRS is to be administered in Part B at screening, Admission (Day -1), ~~on Day 9 prior to resuming Levodopa; and on~~**in the morning of** Days 1~~5~~ **and 8,** and ~~22~~**on Day 14**. In both Parts A and B, the Admission (Day -1) complete MDS-UPDRS is performed only if the time between Screening and Admission is ≥7 days; otherwise, the MDS UPDRS Part III only ~~is~~**(Part A) or Part II and Part III (Part B) are** performed. **Part II of the MDS-UPDRS assesses 13 categories of motor experiences of daily living: speech, salivation and drooling, chewing and swallowing, eating tasks, dressing, hygiene, handwriting, doing hobbies and other activities, turning in bed, tremor, getting out of bed, car, or deep chair, walking and balance, and freezing (Goetz, 2008). Part II of the MDS-UPDRS (motor examination) is to be completed in Part B at 12 and 23 hours**	missing in last protocol version)

Section Number and Title	Original Text:	Changed To:	Rationale:
	of movement (Goetz. 2008). Part III of the MDS-UPDRS (motor examination) is to be completed in Part A at 2, 4, 8, and 12 hours postdose on Days 1, 2, 3, 4, 5, 6, and 7, and in Part B at 2, 3, 4, 8, and 12 hours postdose on Days 1, 2, 3, 4, 5, 6, 7, and 9. If the complete MDS-UPDRS is not performed on Admission due to Admission taking place <7 days after Screening, then Part III only should also take place on Admission (Day -1) for both Parts A and B. MDS-UPDRS is to be assessed within ±10 minutes of the scheduled times through the 4 hour time point and within ±15 minutes of the scheduled times for the 6-hour through 12-hour time points. The MDS-UPDRS is provided in Appendix 4.	**postdose on Days 1, 2, 3, 4, 5, and 6. If the complete MDS-UPDRS is not performed on Admission due to Admission taking place <7 days after Screening, then Part II should also take place on Admission (Day -1) for Part B.** Part III of the MDS-UPDRS 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, global spontaneity of movement (Goetz, 2008). Part III of the MDS-UPDRS (motor examination) is to be completed in Part A at 2, 4, 8, and 12 hours postdose on Days 1, 2, 3, 4, 5, 6, and 7~~, and in Part B at 2, 3, 4, 8, and 12 hours postdose on Days 1, 2, 3, 4, 5, 6, 7, and 9~~. **MDS-UPDRS is to be assessed within ±10 minutes of the scheduled times through the 4 hour time point and within ±15 minutes of the scheduled times for the 6-hour through 12-hour time points. Part III of the MDS-UPDRS (motor examination) is to be completed in Part B at 12 and 23 hours postdose on Days 1, 2, 3, 4, 5, and 6.** If the complete MDS-UPDRS is not performed on Admission due to Admission taking place <7 days after Screening, then Part III ~~only~~ should also take place on Admission (Day -1) for both Parts A and B. ~~MDS-UPDRS is to be assessed~~	

Section Number and Title	Original Text:	Changed To:	Rationale:
		~~within ±10 minutes of the scheduled times through the 4 hour time point and within ±15 minutes of the scheduled times for the 6 hour through 12 hour time points. The MDS-UPDRS is provided in Appendix 4.~~ **All MDS-UPDRS measurements in Part B should be taken during the "on" period (within 2 hours of dosing with antiparkinsonian agent(s)).** **The MDS-UPDRS is provided in Appendix 5.**	
[redacted]	[redacted]	[redacted]	[redacted]

Section Number and Title	Original Text:	Changed To:	Rationale:
	[redacted]	[redacted]	

Section Number and Title	Original Text:	Changed To:	Rationale:
[redacted]	[redacted]	[redacted]	[redacted]

Section Number and Title	Original Text:	Changed To:	Rationale:
		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Section Number and Title	Original Text:	Changed To:	Rationale:
	[redacted]	[redacted]	
[redacted]		[redacted]	[redacted]

Section Number and Title	Original Text:	Changed To:	Rationale:
[redacted]	[redacted]	[redacted]	[redacted]
12.1. Blood Sample Collection	In Part A, plasma samples for PK analysis will be collected predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Day 4; predose on Day 5 and Day 6; predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Day 7; in AM of Day 8; and Day 14. In Part B, plasma samples for PK analysis will be	In Part A, plasma samples for PK analysis will be collected predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Day 4; predose on Day 5 and Day 6; predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Day 7; in AM of Day 8; and Day 14.	Changes made to reflect updated study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
	collected predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Days 1 to 4; 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 the AM on Day 9; and on Days 15 and 22. The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. Samples are to be collected within ±5 minutes of the scheduled sampling time. The Investigator or designee will arrange to have the plasma samples processed, stored, and transported as directed for bioanalysis. An additional PK sample may be collected at any time if clinically indicated and at the discretion of the Investigator (eg, for unusual or severe adverse events). Each sample will be marked with unique identifiers such as the study number, subject number, and the nominal sample time. The date and actual time that the blood sample was taken will be recorded on the eCRF or electronically with a bar code or other method.	**Samples are to be collected within ±5 minutes of the scheduled sampling time.** In Part B, plasma samples for PK analysis will be collected predose and ~~0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Days 1 to 4; 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 the AM on Day 9; and on Days 15 and 22.~~**13 hours postdose on Day 1; and 13 hours postdose on Days 2 through 7, and on Day 14. Samples are to be collected within ±1 hour of the scheduled sampling time.** The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. ~~Samples are to be collected within ±5 minutes of the scheduled sampling time.~~ The Investigator or designee will arrange to have the plasma samples processed, stored, and transported as directed for bioanalysis. An additional PK sample may be collected at any time if clinically indicated and at the discretion of the Investigator (eg, for unusual or severe adverse events). Each sample will be marked with unique identifiers such as the study number, subject number, and the nominal sample time. The date and actual time that the blood sample was taken will be recorded on the eCRF or electronically with a bar code or other method.	

Section Number and Title	**Original Text:**	**Changed To:**	**Rationale:**
13.1. Safety and Tolerability Parameters	Safety and tolerability of study drug will be evaluated by adverse event reporting, vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, and SSS and MOAA/S scores.	Safety and tolerability of study drug will be evaluated by adverse event reporting, vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, and SSS **(Part A only)** and MOAA/S **(Part A only)** scores.	Changes made to reflect updated study design for Part B.
13.1.1. Demographic/Medical History	Age, gender, race, and ethnic origin will be recorded at the Screening visit for Part A. A full medical history, including PD history (eg, time of diagnosis, staging) and medication history, will be recorded at the Screening visit for Part A and updated, as needed, as screening for Part B.	Age, gender, race, and ethnic origin will be recorded at the Screening visit**s** ~~for Part A~~. A full medical history, including PD history (eg, time of diagnosis, **Hoehn and Yahr** staging) and medication history, will be recorded at the Screening visit**s** ~~for Part A and updated, as needed, as screening for Part B~~.	Changes made to reflect updated study design for Part B.
13.1.2. Vital Signs	Vital signs comprise respiratory rate, temperature, and supine (supine for at least 5 minutes prior to the measurement) and standing systolic and diastolic blood pressure and heart rate. In Part A, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in AM of Day 8; and on Day 14. In Part B, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 8; in AM on Day 9; and on Days 15 and 22. Vital signs and pulse oximetry are to be assessed within ±10 minutes of the	Vital signs comprise respiratory rate, temperature, and supine (supine for at least 5 minutes prior to the measurement) and standing systolic and diastolic blood pressure and heart rate. ~~In Part A, v~~**V**ital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in AM of Day 8; and on Day 14. In Part B, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 8; in AM on Day 9; and on Days 15 and 22. Vital signs and pulse oximetry are to be assessed within ±10 minutes of the scheduled times	Changes made to reflect updated study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
	scheduled times through the 4 hour time point and within ±15 minutes of the scheduled times for the 6-hour through 16-hour time points.	through the 4 hour time point and within ±15 minutes of the scheduled times for the 6-hour through 16-hour time points. **In Part B, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, and 12 hours postdose on Days 1 through 7; and on Day 14. Vital signs and pulse oximetry are to be assessed within ±10 minutes of the 1- and 2 hour time points and within ±15 minutes of the 12-hour time point.**	
13.1.4. Physical Examination	A physical examination of all major body systems will be undertaken and recorded at the Screening visits for Parts A and B. Symptom-directed physical examinations will be performed during Part A on Admission (Day -1), Day 1, Day 3, Day 4, Day 6, and Day 8. Symptom-directed physical examinations will be performed during Part B on Admission (Day -1), Day 1, Day 3, Day 4, Day 5, Day 7, Day 8, Day 9, and Day 15.	A physical examination of all major body systems will be undertaken and recorded at the Screening visits for Parts A and B. Symptom-directed physical examinations will be performed during Part A on Admission (Day -1), Day 1, Day 3, Day 4, Day 6, and Day 8. Symptom-directed physical examinations will be performed during Part B on Admission (Day -1), Day 1, Day 3, Day 4, Day ~~5, Day 7, Day 8, Day 9~~**6**, and Day ~~15~~**8**.	Changes made to reflect updated study design for Part B.
13.1.5. Electrocardiogram (ECG)	A supine 12-lead ECG will be performed at the times specified below and the standard intervals recorded as well as any abnormalities. In Part A, the 12-lead ECG will be assessed at screening and Admission (Day -1); predose on Days 1 and 3; predose and 1 and 12 hours postdose on Days 4, 5, 6, and 7; in AM on Day 8; and Day 14.	A supine 12-lead ECG will be performed at the times specified below and the standard intervals recorded as well as any abnormalities. In Part A, the 12-lead ECG will be assessed at screening and Admission (Day -1); predose on Days 1 and 3; predose and 1 and 12 hours postdose on Days 4, 5, 6, and 7; in AM on Day 8; and Day 14. In	Changes made to reflect updated study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
	In Part B, the 12-lead ECG will be assessed at screening and Admission (Day -1); predose and 1 and 12 hours postdose on Days 1 through 8; in AM on Day 9; Days 15 and 22. All time points are relative to the time of dosing. ECGs are to be performed within ±10 minutes of the predose and 1-hour time points and within ±15 minutes of the 12-hour time point.	Part B, the 12-lead ECG will be assessed at screening and Admission (Day -1); predose and 1 and 12 hours postdose on Days 1 ~~through 8; in AM,~~ **3, 5, and 7, and** on Day ~~9; Days 15 and 22~~**14**. All time points are relative to the time of dosing. ECGs are to be performed within ±10 minutes of the predose and 1-hour time points and within ±15 minutes of the 12-hour time point.	
13.1.6. Laboratory Assessments	In Part A, blood samples will be collected for hematology and serum chemistry at the Screening visit, on Admission (Day -1), predose on Days 4, 6, and 8; and on Day 14. Urine samples will be collected in Part A at screening and Admission (Day -1); predose on Day 4 and Day 7; and on Day 14. In Part B, blood samples will be collected at screening and Admission (Day -1); predose on Days 1, 3, 4, 5, 6, and 8; on Day 9 and Day 15. Urine samples will be collected in Part B at screening and Admission (Day -1); predose on Day 4 and Day 8; and on Day 15. Serum and urine samples for pregnancy tests (females only) will also be collected. These assessments should be performed in accordance with the Schedule of Events (Table 2 and Table 3 as outlined individually below. All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, not clinically significant	In Part A, blood samples will be collected for hematology and serum chemistry at the Screening visit, on Admission (Day -1), predose on Days 4, 6, and 8; and on Day 14. Urine samples will be collected in Part A at screening and Admission (Day -1); predose on Day 4 and Day 7; and on Day 14. In Part B, blood **and urine** samples will be collected at screening and Admission (Day - 1); predose on Days ~~1, 3, 4, 5, 6, and 8; on Day 9 and Day 15. Urine samples will be collected in Part B at screening and Admission (Day -1); predose on Day 4 and Day 8; and on Day 15.~~ **4 and 6; and on Day 8 and Day 14. On Day -1 of Part B, two blood samples will be taken: one sample will be sent to the central lab to be analyzed for reporting purposes and one sample is to be analyzed locally for study eligibility with regard to hematology/serum chemistry criteria.** Serum and urine samples for pregnancy tests (females only) will also be collected. These assessments	Changes made to reflect updated study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
	(NCS); or abnormal, clinically significant (CS). Screening results considered abnormal, CS recorded at the Screening visit may make the subject ineligible for the study pending review by the Medical Monitor. Clinical laboratory results that are abnormal, CS during the study but within normal range at baseline and/or indicate a worsening from baseline will be considered adverse events, assessed according to Section 13.2, and recorded in the eCRF.	should be performed in accordance with the Schedule of Events (Table 2 and Table 3 as outlined individually below. All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS). Screening results considered abnormal, CS recorded at the Screening visit may make the subject ineligible for the study pending review by the Medical Monitor. Clinical laboratory results that are abnormal, CS during the study but within normal range at baseline and/or indicate a worsening from baseline will be considered adverse events, assessed according to Section 13.2, and recorded in the eCRF.	
13.1.6.2.	Serum chemistry tests will include serum electrolytes, renal function tests, including creatinine, blood urea nitrogen, bicarbonate or total carbon dioxide, liver function tests, including total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), total protein, and albumin.	Serum chemistry tests will include serum electrolytes, renal function tests, including creatinine, blood urea nitrogen, bicarbonate or total carbon dioxide, liver function tests, including total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), **alkaline phosphatase (Part B only)**, total protein, and albumin.	Changes made to reflect updated study design for Part B.
13.1.6.5. Pregnancy Screen	Females of childbearing potential will be tested for pregnancy at Parts A and B by serum pregnancy test at the Screening visits and by urine pregnancy test on Day -1 (Admissions).	Females of childbearing potential will be tested for pregnancy at Parts A and B by serum pregnancy test at the Screening visits and by urine pregnancy test on Day -1 (Admissions). **For Part B, females of childbearing potential will also be tested for**	Changes made to reflect updated study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
		pregnancy by urine pregnancy test at the follow-up visit on Day 14.	
13.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS)	Suicidality will be monitored during the study using the C-SSRS (Posner 2011). This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicidal ideation and behavior, and a post-baseline evaluation that focuses on suicidality since the last study visit. The C-SSRS includes 'yes' or 'no' responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe). If in the opinion of the Investigator, the subject is showing any suicidal tendency, no further study drug will be administered and the subject will be referred to a psychologist or psychiatrist for further evaluation. This information will be tracked. The "Baseline/Screening" C-SSRS form will be completed on Screening of Part A (lifetime history and past 24 months). In Part A, the "Since Last Visit" C-SSRS form will be completed on Admission (Day 1); 12 hours postdose on Days 1, 2, and 3; predose on Days 4, 5, 6, and 7; and on Days 8 and 14. In Part B, the "Since Last Visit" C-SSRS form will be completed on Admission (Day -1); 12 hours postdose on Day 1 through Day 8; and on Days 9, 15, and 22. The C SSRS is provided in Appendix 10.	Suicidality will be monitored during the study using the C-SSRS (Posner 2011). This scale consists of a baseline evaluation that assesses the lifetime experience of the subject with suicidal ideation and behavior, and a post-baseline evaluation that focuses on suicidality since the last study visit. The C-SSRS includes 'yes' or 'no' responses for assessment of suicidal ideation and behavior as well as numeric ratings for severity of ideation, if present (from 1 to 5, with 5 being the most severe). If in the opinion of the Investigator, the subject is showing any suicidal tendency, no further study drug will be administered and the subject will be referred to a psychologist or psychiatrist for further evaluation. This information will be tracked. The "Baseline/Screening" C-SSRS form will be completed on Screening of Part**s** A **and B** (lifetime history and past 24 months). In Part A, the "Since Last Visit" C-SSRS form will be completed on Admission (Day 1); 12 hours postdose on Days 1, 2, and 3; predose on Days 4, 5, 6, and 7; and on Days 8 and 14. In Part B, the "Since Last Visit" C-SSRS form will be completed on Admission (Day -1); **predose and** 12 hours postdose on Day 1; **12 hours postdose on Days 2** through Day ~~8; and on Days 9,~~	Changes made to reflect updated study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
		~~15,~~**7**; and ~~22~~**on Day 14**. The C -SSRS is provided in Appendix 10.	
13.1.8.	The SSS is 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'. In Part A, the SSS will be administered on Admission (Day -1); predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in the AM on Day 8; and Day 14. All time points are relative to the time of dosing. 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. In Part B, the SSS will be administered on Admission (Day -1); predose on Days 1 through 8; in AM on Day 9; and Days 15 and 22. The SSS should be performed prior to the MOAA/S score. The SSS is provided in Appendix 11.	The SSS is 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'. In Part A, the SSS will be administered on Admission (Day -1); predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in the AM on Day 8; and Day 14. All time points are relative to the time of dosing. 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. ~~In Part B, the SSS will be administered on Admission (Day -1); predose on Days 1 through 8; in AM on Day 9; and Days 15 and 22.~~ The SSS should be performed prior to the MOAA/S score. **The SSS will not be administered in Part B.** The SSS is provided in Appendix 11.	Changes made to reflect updated study design for Part B.
13.1.9.	The MOAA/S allows exploration of deeper sedation states than the SSS. If an 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. In Part A,	The MOAA/S allows exploration of deeper sedation states than the SSS. If an 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. In Part A,	Changes made to reflect updated study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
	the MOAA/S assessment should be conducted after other assessments that are scheduled at the same time point. In Part A, the MOAA/S will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 3, 4, 5, 6, and 7; in AM on Day 8; and Day 14. In Part B, the MOAA/S will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 8; in AM on on Day 9; and Days 15 and 22. The MOAA/S 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 for the 6-hour through 16-hour time points. The MOAA/S is provided in Appendix 12.	the MOAA/S assessment should be conducted after other assessments that are scheduled at the same time point. In Part A, the MOAA/S will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 3, 4, 5, 6, and 7; in AM on Day 8; and Day 14. ~~In Part B, t~~**T**he MOAA/S will **not** be performed ~~predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 8; in AM on on Day 9; and Days 15 and 22~~**in Part B**. ~~The MOAA/S 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 for the 6-hour through 16-hour time points.in Part B.~~ The MOAA/S is provided in Appendix 12.	
13.2.1.1. Adverse Events	An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an adverse event can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered. All adverse events that occur after any subject has been enrolled, before treatment, during treatment, or following the cessation of treatment until the Day 22 Follow-up visit of Part B, whether or not they are	An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an adverse event can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered. All adverse events that occur after any subject has been enrolled, before treatment, during treatment, or following the cessation of treatment until the Day ~~22~~**14** Follow-up visit of Part**s A and** B, whether or	Changes made to reflect updated study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
	related to the study, must be recorded on forms provided by Sage Therapeutics.	not they are related to the study, must be recorded on forms provided by Sage Therapeutics.	
13.2.1.3. Serious Adverse Event	A serious adverse event is an adverse event occurring during any study phase and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following: • It results in death • It is immediately life-threatening • It requires inpatient hospitalization or prolongation of existing hospitalization • It results in persistent or significant disability or incapacity • It results in a congenital abnormality or birth defect • It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. All serious adverse events that occur after any subject has been enrolled, before treatment, during treatment, and until the Day 22 Follow-up visit of Part B, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics.	A serious adverse event is an adverse event occurring during any study phase and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following: • It results in death • It is immediately life-threatening • It requires inpatient hospitalization or prolongation of existing hospitalization • It results in persistent or significant disability or incapacity • It results in a congenital abnormality or birth defect • It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. All serious adverse events that occur after any subject has been enrolled, before treatment, during treatment, and until the Day ~~22~~**14** Follow-up visit of Part**s A and** B, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics.	Changes made to reflect updated study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
13.2.1.4. Recording Sedation as an Adverse Event	Sedation will be assessed using protocol-specified rating scales. In order to standardize the reporting of sedation as adverse events, Investigators must record sedation as an adverse event if there is a score of >5 on the SSS and/or a score of ≤2 on the MOAA/S. Consideration should be given to the most appropriate term to describe the sedation characteristics.	**In Part A and Part B, s**~~S~~edation will be assessed using protocol-specified rating scales. **Consideration should be given to the most appropriate term to describe the sedation characteristics.** **For Part A, i**~~I~~n order to standardize the reporting of sedation as adverse events, Investigators must record sedation as an adverse event if there is a score of >5 on the SSS and/or a score of ≤2 on the MOAA/S. **SSS and MOAA/S do not apply to Part B.** ~~Consideration should be given to the most appropriate term to describe the sedation characteristics.~~	Changes made to reflect updated study design for Part B.
13.5. Reporting Serious Adverse Events	All serious adverse events (regardless of causality) will be recorded from the signing of the ICF until the Day 22 Follow-up visit of Part B. Any serious adverse events considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All serious adverse events must be reported to the Sponsor or Sponsor's designee immediately by phone and in writing within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the serious adverse event pages, verify the accuracy of the information recorded on the serious adverse event pages with the corresponding source	All serious adverse events (regardless of causality) will be recorded from the signing of the ICF until the Day ~~22~~**14** Follow-up visit of Part**s A and** B. Any serious adverse events considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All serious adverse events must be reported to the Sponsor or Sponsor's designee immediately by phone and in writing within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the serious adverse event pages, verify the accuracy of the information recorded on the serious adverse event pages with the corresponding source documents, and send a copy to Sage Therapeutics or designee.	Changes made to reflect updated study design for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
	documents, and send a copy to Sage Therapeutics or designee.		
14.1 Data Analysis Sets	The safety population is defined as all subjects who are administered study drug. The efficacy population will consist of all subjects in the safety population who receive at least one dose of study drug and have at least one postdose MDS-UPDRS evaluation. The PK population will consist of all subjects in the safety population with sufficient plasma concentrations for PK evaluations. Separate populations will be defined for each part of the study.	The safety population is defined as all subjects who are administered **at least one dose of** study drug. **Safety population will be used to provide descriptive summaries of all safety data.** The efficacy population will consist of all subjects in the safety population who receive at least one dose of study drug and have at least one postdose MDS-UPDRS evaluation. **The efficacy population will be used to analyze all efficacy data.** The PK population will consist of all subjects in the safety population with sufficient plasma concentrations for PK evaluations. Separate populations will be defined for each part of the study.	Updated for clarification
14.3. General Considerations		Added section	Section was inadvertently missing in previous version
14.5. Efficacy Endpoints	The primary endpoints of this study relate to safety and tolerability. Efficacy assessments include evaluation of PD symptoms by the MDS-UPDRS, [redacted]	The primary endpoints of ~~this study relate to safety and tolerability. Efficacy assessments include evaluation of PD symptoms by the MDS-UPDRS,~~ [redacted] **Part A relate to safety and**	Changes made to reflect updated endpoints for Part B.

Section Number and Title	Original Text:	Changed To:	Rationale:
		tolerability. The primary endpoint for Part B is to evaluate the improvement in PD tremor as assessed by changes in the 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).	
14.5.1. Secondary Efficacy Endpoints	In Part A, changes in the MDS-UPDRS – Part III score will be summarized overall and by tolerated dose. In Part B, changes in the MDS-UPDRS – Part III total score, and the MDS-UPDRS – Parts I-IV score will be summarized overall and by randomized treatment sequence and tolerated dose.	In Part A, changes in the MDS-UPDRS – Part III score will be summarized overall and by tolerated dose. In Part B, ~~changes in the~~ MDS-UPDRS – Part III total score, and the MDS-UPDRS – Parts I-IV **total** score will be summarized overall and by ~~randomized treatment sequence and~~ tolerated dose.	a) Clarification; b) Change made to reflect updated study design for Part B (no longer randomized)
14.5.2. Exploratory Efficacy Endpoints	[redacted]	[redacted]	[redacted]

Section Number and Title	**Original Text:**	**Changed To:**	**Rationale:**
		[redacted]	
14.6. Safety and Tolerability Analyses	Data from vital signs, clinical laboratory measures, ECG, C-SSRS, SSS, and MOAA/S will be summarized using descriptive statistics by group and time point, where applicable. Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and will be summarized using descriptive statistics. Out-of-range safety endpoints may be categorized as low or high, where applicable. For all categorical endpoints, summaries will include counts and percentages.	Data from vital signs, clinical laboratory measures, ECG, C-SSRS, SSS **(Part A only)**, and MOAA/S **(Part A only)** will be summarized using descriptive statistics by group and time point, where applicable. Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and will be summarized using descriptive statistics. Out-of-range safety endpoints may be categorized as low or high, where applicable. For all categorical endpoints, summaries will include counts and percentages.	Changes made to reflect updated endpoints for Part B
14.6.1. Adverse Events	All adverse events and serious adverse events (including those with onset or worsening before the start of open-label study drug) through the Day 22 Follow-up visit of Part B will be listed.	All adverse events and serious adverse events (including those with onset or worsening before the start of open-label study drug) through the Day ~~22~~**14** Follow-up visit of Part**s A and** B will be listed.	Changes made to reflect updated study design for Part B

Section Number and Title	Original Text:	Changed To:	Rationale:
14.6.7. Stanford Sleepiness Scale (SSS)	Sedation data collected on the SSS will be listed for all subjects. Changes in score over time will be represented graphically, and change from baseline of Part A and Part B will be summarized.	Sedation data collected on the SSS will be listed for all subjects **in Part A**. Changes in score over time will be represented graphically, and change from baseline of Part A ~~and Part B~~ will be summarized.	Changes made to reflect updated endpoints for Part B
14.6.8. Modified Observer's Assessment of Alertness/Sedation (MOAA/S)	Sedation data collected on the MOAA/S will be listed for all subjects. Changes in score over time will be represented graphically, and change from baseline of Part A and Part B will be summarized.	Sedation data collected on the MOAA/S will be listed for all subjects **in Part A**. Changes in score over time will be represented graphically, and change from baseline of Part A ~~and Part B~~ will be summarized.	Changes made to reflect updated endpoints for Part B
14.6.9. Prior and Concomitant Medications	Medications will be recorded at each study visit during the study and will be coded using World Health Organization (WHO)-Drug dictionary September 2015, or later. Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those taken during the 4 weeks prior to the date of the first dose of open-label study drug. Concomitant medications are defined as those with a start date on or after the first dose of open-label study drug, or those 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. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.	Medications will be recorded at each study visit during the study and will be coded using World Health Organization (WHO)-Drug dictionary September 2015, or later. Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those taken during the 4 weeks prior to the date of the first dose of open-label study drug. Concomitant medications are defined as those with a start date on or after the first dose of open-label study drug, or those 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. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.	Changes made to reflect updated study design for Part B

Section Number and Title	Original Text:	Changed To:	Rationale:
	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. The use of rescue medication will be recorded and summarized.	~~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. The use of rescue medication will be recorded and summarized.	
14.8.	Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14. Approximately 12 subjects are anticipated to be randomized to 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.	Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14. ~~Approximately 12 subjects are anticipated to be randomized to Part B.~~**Up to 15 new 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).** 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.	a) Changes made to reflect updated study design for Part B; b) change made to reflect availability of SAGE-217 Capsule
[redacted]		[redacted]	[redacted]

Section Number and Title	Original Text:	Changed To:	Rationale:
		[redacted]	[redacted]
Appendix 4. Tremorogenic Drugs (new appendix)		New appendix added.	Added as reference for new Exclusion Criteria #6 for Part B due to updated study design
[redacted]		[redacted]	[redacted]

1. TITLE PAGE

PROTOCOL NUMBER: 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

IND NUMBER: 131,258

Investigational Product	SAGE-217
Clinical Phase	2
Sponsor	Sage Therapeutics, Inc.
Sponsor Contact	[redacted], M.D., Ph.D. [redacted] Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: [redacted] Email: [redacted]
Medical Monitor	[redacted], M.D., M.P.H. Study Physician Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: [redacted] Email: [redacted]
Date of Original Protocol	28 September 2016
Date of Amendment 1	5 October 2016

Date of Amendment 2 24 October 2017

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

PROTOCOL SIGNATURE PAGE

Protocol Number:	217-PRK-201
Product:	SAGE-217 Oral Solution
IND No.:	131, 258
Study Phase:	2
Sponsor:	Sage Therapeutics
Date of Amendment 2:	Version 3.0 24 October 2016

Sponsor Approval

[redacted], M.D., Ph.D.
Sage Therapeutics
25 October 2016
Date (DD /MMM/YYYY)

[redacted] Pharm.D, M.S., R.Ph.
Jsozk uotb
Date (D D/MMM/YYYY)

[redacted] H.S.
Sage Therapeutics
25 Oct 2016
Date (DD/MMWYY YY)

[redacted] PhD
Sage Therapeutics
25 Oct 2016
Date (DD/MM:vt/YYYY)

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the Clinical Protocol 217-PRK-201 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

CONTACTS IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Research Organization	[redacted]	[redacted]

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics
215 First Street
Cambridge, MA 02142

Name of Investigational Product:
SAGE-217 Oral Solution

Name of Active Ingredient:
SAGE-217

Title of Study: 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 (PD) of Moderate Severity Responding to Immediate-Release Levodopa/Carbidopa and Withdrawn from Levodopa/Carbidopa

Study centers: Up to 4 centers

Objectives:

Primary:

- To evaluate the safety and tolerability of SAGE-217 Oral Solution.

Secondary:

- 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.
- To compare the effect of SAGE-217 Oral Solution in combination with immediate-release oral Levodopa/Carbidopa to Levodopa/Carbidopa alone.

Endpoints:

Primary:

- Frequency and severity of adverse events and changes 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.

Secondary:

Part A:

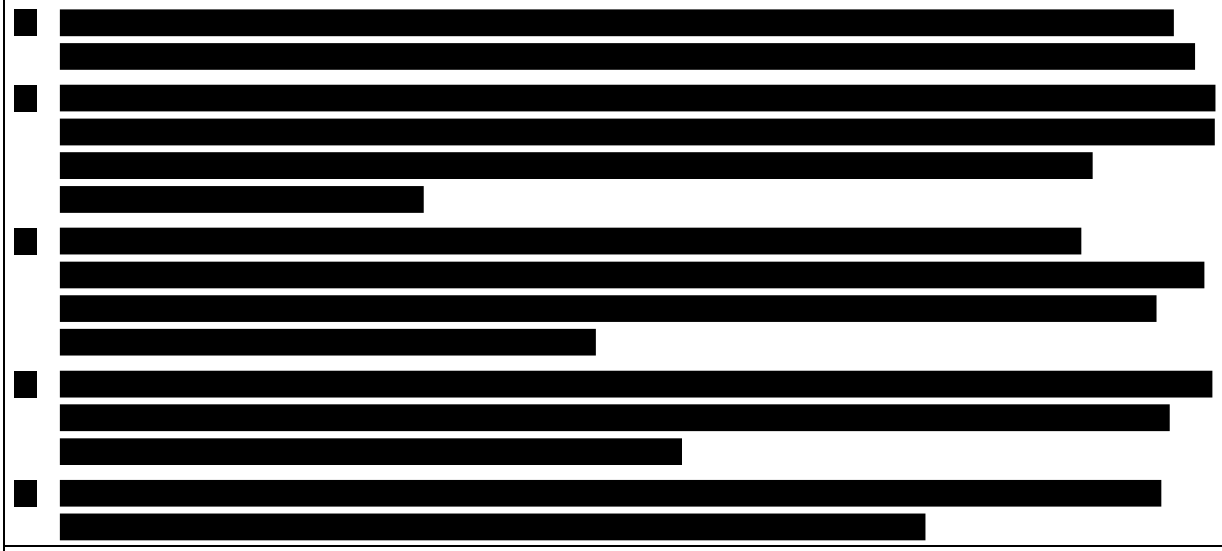
- Improvement in PD motor symptoms as assessed by changes in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) – Part III (Motor Examination) score.

Part B:

- Improvement in PD motor symptoms as assessed by changes in the MDS-UPDRS – Part III score.
- Improvement in PD overall symptoms as assessed by changes in the MDS-UPDRS – Parts I-IV total score.
- Sleepiness/sedation as assessed by the Stanford Sleepiness Scale (SSS) and Modified Observer's Assessment of Analgesia/Sedation (MOAA/S) scores.

In addition, plasma concentrations of SAGE-217 and possibly SAGE-217 metabolites will be measured, and pharmacokinetic (PK) parameters will be derived.

Exploratory Endpoints:



Methodology:

This study will assess the safety, tolerability, PK, and efficacy of SAGE-217 Oral Solution. For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol.

There are two parts:

Part A: Open-label with morning (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 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. Subjects not tolerating 30 mg will receive 20 mg, and subjects not tolerating 20 mg will receive 10 mg on subsequent days. 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 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 interim analysis.

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. Subjects randomized to the combination arm of Levodopa and SAGE-217 Oral Solution will receive this combination in the morning for the first 4 days (Days 1 to 4). Subjects randomized to the Levodopa plus placebo arm will receive Levodopa and SAGE-217 matching placebo oral solution 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).

All doses of SAGE-217 Oral Solution (or placebo) will be administered in the morning with food. If subjects are taking Levodopa as opposed to Carbidopa-Levodopa, administration with or without food will be determined by the Investigator.

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 adverse event 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 defined as 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 (Table 2 and Table 3, respectively).

Number of patients (planned):

Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14 to inform the conduct of Part B. Twelve subjects are anticipated to be randomized in Part B.

Diagnosis and main criteria for inclusion: All of the following inclusion and exclusion criteria will be applied during screening for Part A, with some of the criteria applied during screening for Part B, as indicated.

Inclusion criteria:

1. Subject has signed an informed consent form (ICF) before any study-specific procedures are performed.
2. Subject is between 40 and 75 years of age, inclusive.
3. Subject has a diagnosis of idiopathic PD based on modified UK Brain Bank Criteria (modified to allow individuals with a family history of PD) (Hughes 1992; Appendix 1).

4. Subjects with PD with a duration of less than 7 years and must meet the criteria for Hoehn and Yahr stage 2 or stage 3 (Appendix 2).
5. Subject has a stable dose of antiparkinsonian agents including immediate-release oral Levodopa or Carbidopa-Levodopa (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.
6. Subject is willing to discontinue his/her treatment with immediate-release oral Levodopa or Carbidopa-Levodopa for at least 8 hours prior to dosing with SAGE-217. (Part B also)
7. Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) or amantadine at least 5 days prior to the day of admission (Day -1). (Part B also)
8. Subjects taking an antidepressant drug, sleep medication, or neuroleptic must have been on a stable dose for at least 1 month prior to the baseline visit.
9. Subjects must have a MoCA score of >22.
10. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests. (Part B also)
11. Female subjects must agree to practice a highly effective method of birth control while on study through completion of the last follow-up visit. If a subject discontinues early after receiving a dose of SAGE-217, then the subject must continue this method of birth control for at least 7 days following the last dose of study drug. Highly effective methods of birth control include combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence. (Part B also)
12. Male subjects must agree to practice a highly effective method of birth control while on study, and for 13 weeks after receiving the last dose of study drug. Effective methods of birth control include sexual abstinence, vasectomy, or a condom with spermicide (men) in combination with their partner's highly effective method. (Part B also)
13. Males must be willing to abstain from sperm donation and females from donating eggs while on study through 13 weeks after receiving the last dose of study drug. (Part B also)

Exclusion criteria:

1. Subjects with a known hypersensitivity to SAGE-217 Oral Solution or its major excipient, HPβCD. (Part B also)
2. Subjects with early PD (Hoehn and Yahr stage 1) or advanced PD (Hoehn and Yahr stage 4 or stage 5).
3. Subjects with any medical or psychiatric condition that jeopardizes/compromises his/her ability for participation. This includes schizophrenia spectrum and other psychotic disorders, substance-related and addictive disorders, feeding and eating disorders, bipolar and related disorders, structural brain disease including but not limited to history of encephalitis or hydrocephalus and history of clinically significant stroke, or anticipating starting psychotherapy or behavior therapy during the course of the study or who started psychotherapy or behavior therapy within 30 days prior to Part A Day 1.
4. Subjects with a history of:
   a. Electroconvulsive therapy;
   b. Stereotaxic brain surgery (deep brain stimulation) for PD;
   c. History of suicide attempt within 2 years, or has answered YES to questions 3, 4, or 5 on the C SSRS at the screening or Day -1 visits, or has current suicidal ideation; or

d. Impulse control disorder.

5. Subjects with severe depression as defined by a BDI-II score >19.
6. Subjects with Type I or Type II diabetes mellitus.
7. Subjects with presence of drug-induced parkinsonism (eg, metoclopramide, flunarizine), metabolic identified neurogenetic disorders (eg, Wilson's disease), encephalitis, or other atypical Parkinsonian syndromes (eg, progressive supranuclear palsy, multiple system atrophy). (Part B also)
8. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease. (Part B also)
9. Subject has clinically significant abnormal physical examination OR 12-lead ECG at the screening or admission visits. NOTE: QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study. ECG may be repeated once if initial values obtained are outside the specified limits. (Part B also)
10. Subject has a history, presence and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies 1 and 2.
11. Subject has exposure to another investigational medication or device within 30 days prior to Part A Day 1.
12. Subject has donated one or more units of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing (1 unit = 450 mL). (Part B also)
13. Subject is unwilling or unable to comply with study procedures. (Part B also)
14. Subjects has used any known strong inhibitors and/or inducers of cytochrome P450 (CYP)3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug. (Part B also)

Investigational product, dosage and mode of administration:

SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dose.

Duration of treatment: 7 days in Part A; 8 days in Part B

Part A:

Screening duration: up to 28 days; Treatment Period: 7 days (SAGE-217 dosing for 4 days); Follow-up: 7 days

Planned participation per subject: approximately 42 days during Part A.

Part B:

Screening duration: up to 14 days; Treatment Period: 8 days; Follow-up: 14 days

Planned participation per subject: approximately 36 days during Part B.

Reference therapy, dosage and mode of administration:

In part B, placebo will be taste-matched to SAGE-217 Oral Solution.

Criteria for evaluation:

Safety and tolerability:

Safety and tolerability of study drug will be evaluated by vital signs, clinical laboratory measures, ECGs, physical examinations, concomitant medication usage, C-SSRS, and adverse event reporting. Sleepiness/sedation will be assessed by the SSS and MOAA/S.

Efficacy:

Improvement in PD motor symptoms and overall symptoms will be assessed by changes in the MDS-UPDRS Part III score and MDS-UPDRS Parts I-IV total score at various time points.

Pharmacokinetics:

Plasma will be collected to assay for concentrations of SAGE-217 and possibly SAGE-217 metabolites. The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), the distributional half-life and terminal half-life ($t_{1/2}$), and steady-state drug concentration in the plasma (C_{ss}).

Statistical methods:

Study Populations

The safety population, defined as all subjects who are administered study drug, will be used to provide descriptive summaries of safety.

The efficacy population, defined as all subjects in the safety population who receive at least one dose of study drug and have at least one postdose MDS-UPDRS evaluation, will be used to analyze efficacy data.

The PK population will consist of all subjects in the safety population with sufficient plasma concentrations for PK evaluations and will be used to summarize PK data.

Separate populations will be defined for each part of the study.

General Considerations

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

Safety Analysis

Adverse events will be coded using Medical Dictionary for Regulatory Activities™ (MedDRA). The overall incidence of adverse events will be displayed by System Organ Class (SOC), preferred term, dose group, and cohort. Incidence of adverse events will also be presented by maximum severity and relationship to study drug. Vital signs, clinical laboratory measures, ECG, and C-SSRS data will be summarized by dose group and cohort, where applicable. Out-of-range safety endpoints may be categorized as low or high, where applicable.

Efficacy Analysis

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data.

An interim analysis of 10 subjects completing Part A is planned to inform Part B study conduct.

Pharmacokinetic Analysis

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics and listed by subject.

Table 2: Schedule of Events: Part A (Open-Label)

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		

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)
[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 Admission (Day -1); predose for Day 4, Day 6, and Day 8; and Day 14

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

[d] Vital Signs: Screening and 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. 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 be used 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 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 Part III only should also take place on Admission (Day -1).

[redacted]

[p] Plasma PK sampling times (±5 minutes): Day 4 predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose; predose 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

Table 3: Schedule of Events: Part B (Randomized, Placebo-Controlled)

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]													

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
[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]; 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).

[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.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

1. TITLE PAGE 1
2. SYNOPSIS 6
3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 18
4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 25
5. INTRODUCTION 27
5.1. Background of Parkinson's Disease and Unmet Medical Need 27
5.2. SAGE-217 Oral Solution 28
5.3. Summary of Nonclinical and Clinical Experience with SAGE-217 28
5.3.1. Nonclinical Studies with SAGE-217 28
5.3.2. Clinical Experience 28
5.4. Potential Risks and Benefits 30
6. TRIAL OBJECTIVES AND PURPOSE 31
6.1. Primary Objective 31
6.2. Secondary Objectives 31
6.3. Endpoints 31
6.3.1. Primary Endpoints 31
6.3.2. Secondary Endpoints 31
6.3.3. Exploratory Endpoints 31
7. INVESTIGATIONAL PLAN 33
7.1. Overall Study Design 33
7.2. Number of Subjects 34
7.3. Treatment Assignment 34
7.4. Dose Adjustment Criteria 35
7.5. Criteria for Study Termination 35
8. SELECTION AND WITHDRAWAL OF SUBJECTS 37
8.1. Subject Inclusion Criteria 37
8.2. Subject Exclusion Criteria 38
8.3. Entrance Criteria for Part B 39
8.4. Subject Withdrawal Criteria 39

9. TREATMENT OF SUBJECTS 41
9.1. Description of Study Drug 41
9.1.1. Part A 41
9.1.2. Part B 41
9.2. Concomitant Medications 41
9.2.1. Prior/Concomitant Medications 41
9.2.2. Prohibited Medications 42
9.3. Treatment Compliance 42
9.4. Randomization and Blinding 42
10. STUDY DRUG MATERIALS AND MANAGEMENT 44
10.1. Study Drug 44
10.2. Study Drug Packaging and Labeling 44
10.3. Study Drug Storage 44
10.4. Study Drug Preparation 45
10.5. Administration 45
10.6. Study Drug Accountability 46
10.7. Study Drug Handling and Disposal 46
11. ASSESSMENT OF EFFICACY 47
11.1. Movement Disorder Society – Unified Parkinson's Disease Rating Scale 47
11.2. Exploratory Endpoints 48
[redacted] [redacted] 48
[redacted] [redacted] 48
[redacted] [redacted] 48
[redacted] [redacted] 49
[redacted] [redacted] 50
12. PHARMACOKINETICS 51
12.1. Blood Sample Collection 51
12.2. Storage and Shipment of Pharmacokinetic Samples 51
12.3. Sample Analysis 51
13. ASSESSMENT OF SAFETY 52
13.1. Safety and Tolerability Parameters 52
13.1.1. Demographic/Medical History 52
13.1.2. Vital Signs 52

13.1.3. Weight and Height 52
13.1.4. Physical Examination 52
13.1.5. Electrocardiogram (ECG) 52
13.1.6. Laboratory Assessments 53
13.1.6.1. Hematology 53
13.1.6.2. Blood Chemistry 53
13.1.6.3. Urinalysis 53
13.1.6.4. Virus Serology 53
13.1.6.5. Pregnancy Screen 53
13.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS) 54
13.1.8. Stanford Sleepiness Scale (SSS) 54
13.1.9. Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) 54
13.2. Adverse and Serious Adverse Events 55
13.2.1. Definition of Adverse Events 55
13.2.1.1. Adverse Event 55
13.2.1.2. Suspected Adverse Reaction 55
13.2.1.3. Serious Adverse Event 55
13.2.1.4. Recording Sedation as an Adverse Event 56
13.2.2. Pregnancy 56
13.3. Relationship to Study Drug 56
13.4. Recording Adverse Events 57
13.5. Reporting Serious Adverse Events 57
14. STATISTICAL METHODS AND CONSIDERATIONS 59
14.1. Data Analysis Sets 59
14.2. Handling of Missing Data 59
14.3. Demographics and Baseline Characteristics 59
14.4. Efficacy Endpoints 59
14.4.1. Secondary Efficacy Endpoints 59
14.4.2. Exploratory Efficacy Endpoints 59
14.5. Safety and Tolerability Analyses 60
14.5.1. Adverse Events 60
14.5.2. Vital Signs 60
14.5.3. Physical Examinations 60

14.5.4. 12-Lead ECG 60
14.5.5. Clinical Laboratory Evaluations 61
14.5.6. Columbia-Suicide Severity Rating Scale (C-SSRS) 61
14.5.7. Stanford Sleepiness Scale (SSS) 61
14.5.8. Modified Observer's Assessment of Alertness/Sedation (MOAA/S) 61
14.5.9. Prior and Concomitant Medications 61
14.6. Pharmacokinetic Analysis 61
14.7. Determination of Sample Size 62
14.8. Changes From Protocol Specified Analyses 62
15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS 63
15.1. Study Monitoring 63
15.2. Audits and Inspections 63
15.3. Institutional Review Board (IRB) 64
16. QUALITY CONTROL AND QUALITY ASSURANCE 65
17. ETHICS 66
17.1. Ethics Review 66
17.2. Ethical Conduct of the Study 66
17.3. Written Informed Consent 66
18. DATA HANDLING AND RECORDKEEPING 67
18.1. Inspection of Records 67
18.2. Retention of Records 67
18.3. Confidentiality 67
19. PUBLICATION POLICY 69
20. LIST OF REFERENCES 70
21. APPENDICES 72
APPENDIX 1. UNITED KINGDOM BRAIN BANK CRITERIA 73
APPENDIX 2. HOEHN AND YAHR STAGING CRITERIA 74
APPENDIX 3. ANTICHOLINERGIC DRUGS 75
APPENDIX 4. MOVEMENT DISORDER SOCIETY-UNIFIED PARKINSON'S DISEASE RATING SCALE (MDS-UPDRS) 76
[redacted] 77
[redacted] 78
[redacted] 81

[redacted] [redacted] 84

APPENDIX 9. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION AND SINCE LAST VISIT VERSION 87

APPENDIX 10. STANFORD SLEEPINESS SCALE (SSS) 93

APPENDIX 11. MODIFIED OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (MOAA/S) 94

LIST OF TABLES

Table 1: Emergency Contact Information....5
Table 2: Schedule of Events: Part A (Open-Label) 12
Table 3: Schedule of Events: Part B (Randomized, Placebo-Controlled) 15
Table 4: Abbreviations and Specialist Terms 25
Table 5: Batch Formula for 125 mL of Stock SAGE-217 Oral Solution 6 mg/mL....45
Table 6: Rating Scale for the MDS-UPDRS....47

LIST OF FIGURES

Figure 1: Study Design of Part A 36
Figure 2: Study Design of Part B 36

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ALT	alanine aminotransferase
AM	morning
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
[redacted]	[redacted]
BMI	body mass index
CBC	complete blood count
C_{max}	maximum plasma concentration
CRF	case report form
CS	clinically significant
Css	steady-state drug concentration in the plasma
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic CRF
EP	European Pharmacopeia
GABA	γ aminobutyric acid
$GABA_A$	γ aminobutyric acid-ligand gated chloride channel
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPβCD	hydroxypropyl-β-cyclodextrin
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
Levodopa/Carbidopa	Levodopa or Carbidopa-Levodopa
MDS	Movement Disorder Society
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
MoCA	Montreal Cognitive Assessment
MTD	maximum tolerated dose
n	number
NCS	not clinically significant
NF	National Formulary
PD	Parkinson's disease
[redacted]	[redacted]
PK	pharmacokinetic(s)
PM	evening
QTcF	QT interval calculated using the Fridericia method
SOC	system organ class
SRC	Safety Review Committee
SSS	Stanford Sleepiness Scale
TEAE	treatment-emergent adverse event
$t_{1/2}$	terminal half-life
t_{max}	time to reach maximum concentration
USP	United States Pharmacopeia
WHO	World Health Organization

5. INTRODUCTION

5.1. Background of Parkinson's Disease and Unmet Medical Need

Parkinson's disease (PD) is a chronic progressive neurodegenerative condition that affects the motor, autonomic, cognitive, and sensory systems. Parkinson's disease is the second most common neurodegenerative disorder (Bergman 2002) and is associated with a massive loss of dopaminergic cells in the substantia nigra, leading to dopamine hypofunction and alteration of the basal ganglia circuitry. Dopamine neurons are under the control of the excitatory glutamatergic and inhibitory γ-aminobutyric acid (GABA) systems. Imbalance between the glutamatergic and GABA systems may contribute to excitotoxicity and dopaminergic cell death.

The motor symptoms of PD have been linked with a loss of dopamine neurons in the substantia nigra pars compacta and a consequential reduction in the level of dopamine input in the striatum (Siderowf 2012). These symptoms evolve slowly and are characterized by the progression of tremor, rigidity, bradykinesia, and postural instability. Tremor caused by PD can appear as either a resting tremor or an action tremor. The most typical tremor of PD is a "pill-rolling" rest tremor between the thumb and index finger. Not everyone with PD develops a tremor, and those who do experience tremor may have symptoms that come and go. Typically, PD tremor starts in the fingers of one hand before spreading to affect the rest of the arm. Tremor can also spread to affect the foot on the same side of the body and, after several years, the tremor can spread to affect the other side of the body. Without treatment, PD tremor usually worsens over time.

At present, there is no cure for PD. The core symptoms are caused by the degeneration of dopamine-producing neurons and, therefore, treatment consists of dopamine replacement. While enormous progress has been made in the treatment of PD over the past half century, levodopa remains the most potent drug for controlling PD symptoms (Jankovic 2008). The addition of carbidopa, a peripheral dopa decarboxylase inhibitor, enhances the therapeutic benefits of levodopa. However, levodopa therapy is frequently associated with motor complications, and the appropriate time to initiate levodopa therapy continues to be debated (Stern 2004; Weiner 2004). The majority of patients treated with levodopa experience motor fluctuation, dyskinesia or other complications after 5 years of treatment (Jankovic 2005).

Neurosteroids, a group of steroid hormones synthesized in the brain, modulate the function of several neurotransmitter systems. The substantia nigra expresses high concentrations of allopregnanolone, a neurosteroid that positively modulates the action of GABA at γ-aminobutyric acid-ligand gated chloride channel ($GABA_A$) receptors. In PD patients, decreased plasma and cerebrospinal fluid levels of the neurosteroid allopregnanolone and 5α-dihydroprogesterone have been observed (di Michele 2003).

Parkinson's disease is the second most common chronic neurodegenerative disease, affecting about 1 million people in the United States and more than 4 million people worldwide. It has a devastating effect on patients and is often accompanied by tremendous physical and emotional burden not only for the patients but also for their families and friends. As the size of the elderly population grows, the burden of PD is projected to grow substantially over the next few decades. To date, the therapy of PD is symptomatic, aimed at ameliorating motor symptoms. Although the goal of therapy is to reverse the functional disability, abolition of all symptoms and signs is not currently possible, even with high doses of medication. Thus, there is a growing need for

innovative new treatments to prevent, delay onset, or alleviate symptoms of PD. Neurosteroids act as neuroprotectants and as $GABA_A$-receptor agonists in the physiology and pathology of the basal ganglia, impact dopaminergic cell activity and survival, and may therefore represent potential therapeutics in PD.

5.2. SAGE-217 Oral Solution

SAGE-217 is a positive allosteric modulator of the $GABA_A$ receptor and thus is expected to be of benefit for the treatment of PD.

SAGE-217 Oral Solution 6 mg/mL (40% w/w aqueous hydroxypropyl-β-cyclodextrin [HPβCD] with 0.025 mg/mL sucralose) is a non-viscous, clear solution.

5.3. Summary of Nonclinical and Clinical Experience with SAGE-217

5.3.1. Nonclinical Studies with SAGE-217

In nonclinical studies of SAGE-217, sedative-hypnotic effects were consistently observed at higher doses in both in vivo pharmacology studies and in toxicology studies. The sedative-hypnotic impairments seen with SAGE-217 were typical for $GABA_A$-positive modulators, ranging from hyperexcitability and ataxia at the lower doses through deep sedation and ultimately anesthesia at higher doses. Depth and duration of sedation demonstrated a clear dose response over the range tested, with evidence of tolerance occurring with continued exposure. Tolerance to the effects of SAGE-217 on motor incoordination was not observed after 7 days of dosing.

The compound has been assessed in 14-day rat and dog toxicology studies with daily administration of SAGE-217 as a solution in HPβCD in dogs and Labrasol® in rats. The no observed adverse effect level was 3 mg/kg (females) and 22.5 mg/kg (males) in rats and 2.5 mg/kg in dogs. There were no adverse effects in dogs or rats in the main toxicology studies. A single observation of mortality occurred in one female rat at the high dose in a toxicokinetic study that was suspected to have been related to exaggerated pharmacology. Additional toxicology and pharmacology information is provided in the Investigator's Brochure.

5.3.2. Clinical Experience

To date, two clinical studies employing SAGE-217 Oral Solution are clinically complete and final clinical study reports are pending. Discussions of pharmacokinetic (PK) data are limited to the single-ascending dose, food effect, and essential tremor cohorts from Study 217-CLP-101 and the multiple-ascending dose and drug-drug interaction cohorts from Study 217-CLP-102. Discussions of safety data are limited to the single-ascending dose cohorts in Study 217 CLP 101 and the multiple-ascending dose cohorts in Study 217-CLP-102.

Study 217-CLP-101 was a first-in-human, four-part study that assessed the effects of a single dose of SAGE-217. The study was a double-blind, placebo-controlled, single-ascending dose design in healthy adult volunteers, with the objective of identifying the maximum tolerated dose (MTD) and PK profiles of SAGE-217 Oral Solution. Subjects in each of the single-ascending dose cohorts received a single dose of study drug, either SAGE-217 (six subjects) or placebo (two subjects), with SAGE-217 doses of 0.25 mg, 0.75 mg, 2 mg, 5.5 mg, 11 mg, 22 mg, 44 mg, 55 mg, and 66 mg. Escalation to the next dose was undertaken only after safety and PK data

were reviewed by the Safety Review Committee (SRC) and agreement reached that it was safe to increase the dose. The MTD was determined to be 55 mg. Two cohorts, 6 subjects each, received SAGE-217 Oral Solution in an open-label manner (one cohort received 50% of the MTD [22 mg] to study the food effects and the other cohort received the MTD [55 mg] to study the effects on subjects with essential tremor). SAGE-217 Oral Solution was orally bioavailable, demonstrated dose-linear PK from the lowest (0.25 mg) through the highest (66 mg) dose, and supported once-daily oral dosing with food. In addition, the pharmacodynamic effects of the SAGE-217 Oral Solution MTD were assessed in placebo-controlled, blinded, crossover electroencephalogram cohorts of 8 subjects each; one cohort received 50% of the MTD (22 mg) and the other received the MTD (55 mg).

Study 217-CLP-102 was a two-part study that assessed the effects of multiple-ascending doses of SAGE-217 Oral Solution. The study was a double-blind, placebo-controlled, multiple-ascending dose study in healthy adult volunteers. Subjects in each of the multiple-ascending dose cohorts received study drug, either SAGE-217 (nine subjects) or placebo (three subjects), once daily for 7 days, with SAGE-217 Oral Solution doses of 15 mg, 30 mg, and 35 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the SRC and agreement reached that it was safe to increase the dose. The MTD was determined to be 30 mg. It was observed that subjects receiving the drug in the evening did better in terms of tolerability compared to when they received the drug in the morning. A fourth cohort of 12 subjects received 30 mg of SAGE-217 Oral Solution in an open-label manner to study drug-drug interactions. SAGE-217 Oral Solution is not likely to induce the metabolism of cytochrome P450 (CYP)2B6 or CYP3A4 substrates. SAGE-217 Oral Solution was orally bioavailable and suitable for once-daily oral dosing at night time with food.

SAGE-217 Oral Solution was generally well tolerated. In both Phase 1 studies (217-CLP-101 and 217-CLP-102), doses were escalated until the stopping criteria were met. Most adverse events were reported as mild or moderate in intensity, and there were no serious adverse events reported in either study. In addition, none of the observed adverse events resulted in discontinuation of the study drug. At doses planned for further study, the observed sedation was mild, transient, and associated with daily peak exposure. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, dizziness, euphoric mood, fatigue, tremor, and muscle twitching, reported most frequently in the highest dose group (66 mg). Some changes in mean blood pressure and heart rate were observed after single doses of 44 mg and greater. After multiple doses of 30 mg (morning [AM] or evening [PM]) or 35 mg (AM) over 7 days, there was no evidence of changes in mean vital sign measures even though Day 7 plasma concentrations approximated that of the highest single dose in the single-ascending dose study. Subjects seemed to tolerate SAGE-217 better when given as night time dosing.

Neuroactive steroids are a class of endogenous and synthetic positive allosteric modulators that target both synaptic and extra-synaptic $GABA_A$ receptors (Belelli 2002 and confirmed in the Sponsor's in vitro studies). This diverse activity profile suggests that neuroactive steroid $GABA_A$ receptor-positive allosteric modulators could exhibit robust activity against essential tremor. Administration of SAGE-547 injection, a proprietary formulation of the endogenous neuroactive steroid, resulted in significant reductions in upper limb kinetic tremor scores compared to placebo in a Phase 2 proof‑of‑principle study (IND 122,280). Based on these results with SAGE-547, the study design for single-ascending dose study 217-CLP-101 included

a cohort of subjects with essential tremor (N=6) who received SAGE-217 Oral Solution (55 mg) in an open-label manner. Data from this cohort indicate that single doses of SAGE-217 Oral Solution resulted in a reduction in the tremor symptoms, suggesting that SAGE-217 might be effective in treating PD.

There are no clinical efficacy data of SAGE-217 Oral Solution in PD, since the present study is the first study in this indication.

5.4. Potential Risks and Benefits

Protocol 217-PRK-201 is the first clinical study evaluating the efficacy of SAGE-217 Oral Solution in PD. Thus, the potential benefits in this population are unknown, although the risks are likely to be similar to those mentioned in the Investigator's Brochure. GABA compounds that cross the blood-brain barrier or increase GABA activity alleviate muscle stiffness caused by a lack of GABAergic tone (Winkler 1999), validating this receptor as a therapeutic target. Given the promising clinical data with another neuroactive steroid (SAGE-547) in conjunction with the shared broad receptor selectivity profile, oral bioavailability, long half-life, preclinical evidence of anxiolytic activity, and safety data of SAGE-217, it is possible that patients may have a clinical benefit at the exposures selected for this study. In view of the few risks associated with administration of SAGE-217 Oral Solution that have been identified to date, an intra-patient dose-reduction design has been chosen to permit reduction in dose based on tolerability (adverse events), specifically sedation, versus treatment effect. Each subject will start with an initial dose of 30 mg; subjects unable to tolerate 30 mg will receive 20 mg; subjects unable to tolerate 20 mg will receive 10 mg. The tolerated dose for each subject will be the dose taken on Day 7. Subjects who tolerate at least the 10 mg dose on Day 7 will be eligible to enroll in Part B. Given the high medical need and potential for benefit in PD, there is a favorable benefit-risk evaluation to investigate SAGE-217 Oral Solution in PD.

In conclusion, selection criteria for the proposed study take into account the potential safety risks. Continuous safety monitoring, and the implementation of a formal dose-reduction and study drug discontinuation scheme also have the potential to mitigate risk. From a benefit/risk perspective, the appropriate measures are being taken in order to ensure the safety of the subjects who will be enrolled.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of SAGE-217 Oral Solution.

6.2. Secondary Objectives

The secondary objectives of the study 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.
- To compare the effect of SAGE-217 Oral Solution in combination with immediate-release oral Levodopa/Carbidopa to Levodopa/Carbidopa alone.

6.3. Endpoints

6.3.1. Primary Endpoints

- Frequency and severity of adverse events and changes 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.

6.3.2. Secondary Endpoints

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) score.

Part B:

- Improvement in PD motor symptoms as assessed by changes in the MDS-UPDRS – Part III score.
- Improvement in PD overall symptoms as assessed by changes in the MDS-UPDRS – Parts I-IV total score.
- Sleepiness/sedation as assessed by the Stanford Sleepiness Scale (SSS) and Modified Observer's Assessment of Analgesia/Sedation (MOAA/S) scores.

6.3.3. Exploratory Endpoints

[redacted]

[redacted]

7. INVESTIGATIONAL PLAN

For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol.

7.1. Overall Study Design

This study is a two-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 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 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 morning with food, as outlined in Section 9.1.1. 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). 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 interim analysis.

  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 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. Subjects randomized to the Levodopa plus placebo arm will receive Levodopa and SAGE-217 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 adverse event 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 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 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.

The study designs of Part A and Part B are displayed in Figure 1 and Figure 2, respectively. Assessments will be performed periodically during the study as outlined in the Schedule of Events for Part A and Part B (Table 2 and Table 3, respectively).

7.2. Number of Subjects

Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14 to inform the conduct of Part B. Twelve subjects are anticipated to be randomized in Part B.

7.3. Treatment Assignment

SAGE-217 will be administered in the morning with food in Parts A and B. Food intake will be standardized as specified by the Sponsor. If subjects are taking Levodopa as opposed to Carbidopa-Levodopa, administration with or without food will be determined by the Investigator.

Part A of the study is open-label. Part B of the study is randomized, placebo-controlled, two-sequence crossover. Subjects will be randomly assigned in a 1:1 manner to receive open-label Levodopa plus blinded SAGE-217 Oral Solution or placebo for 4 days (Days 1 to 4, Period 1 of crossover). Subjects, clinicians, and the study team will be blinded to treatment allocation. The pharmacist, who will prepare the oral solutions according to the randomization schedule, will be unblinded. For the remaining 4 days of Part B (Days 5 to 8, Period 2 of crossover), all subjects

will discontinue Levodopa and will receive their individually established tolerated dose of SAGE-217 Oral Solution from Part A in an open-label manner.

Dose reductions for lack of tolerability will be allowed during both parts of the study (Section 7.4).

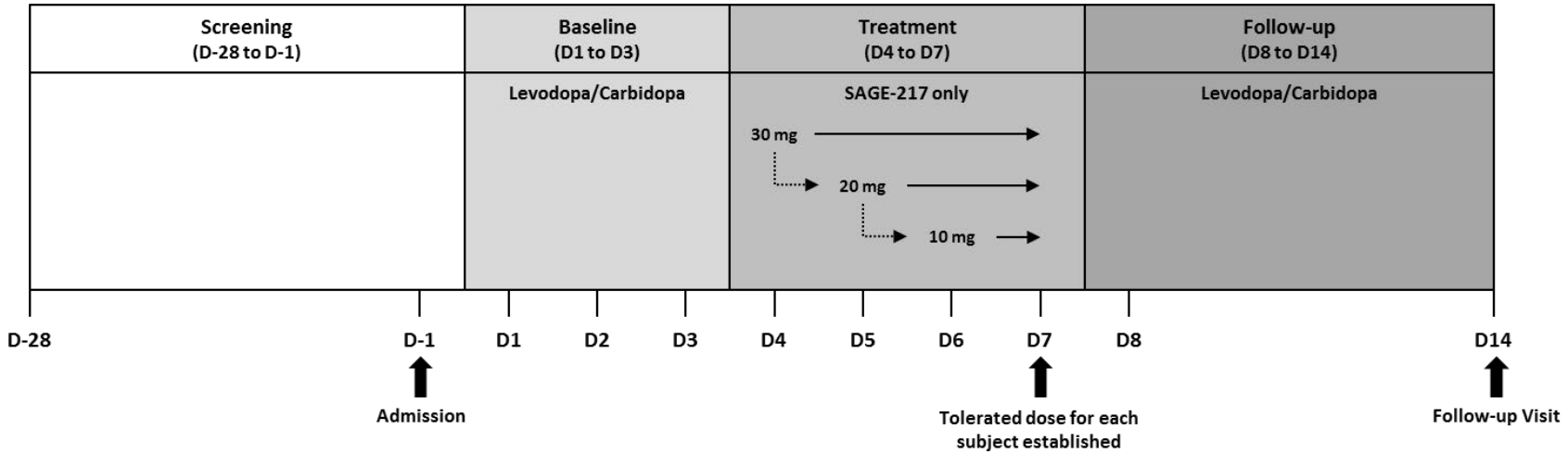
7.4. Dose Adjustment Criteria

Dose reductions of SAGE-217 for lack of tolerability will be allowed during both parts of the study. If at any time the dose is not tolerated in Part A, as determined by the Investigator, the dose on the next day will be reduced to the next lowest dose (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 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

7.5. Criteria for Study Termination

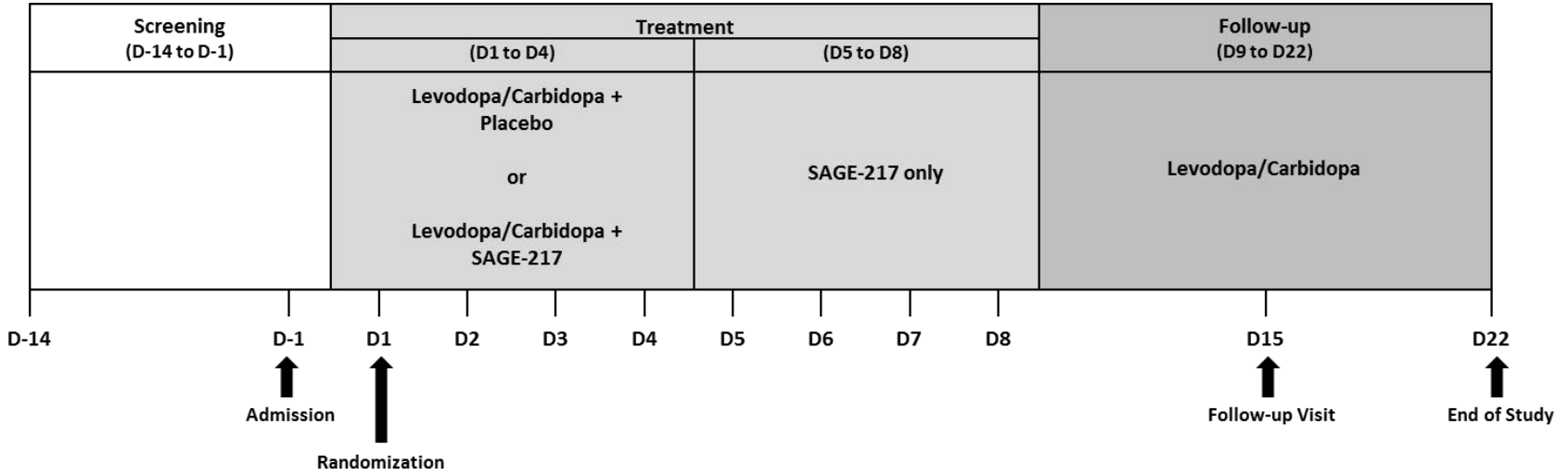
Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons, including the occurrence of adverse events or other findings suggesting unacceptable risk to subjects, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their Institutional Review Board (IRB) and initiate withdrawal procedures for participating subjects.

Figure 1: Study Design of Part A



NOTE: In order to qualify for Part B of the study, a subject must tolerate a dose of at least 10 mg of SAGE-217 Oral Solution in Part A.

Figure 2: Study Design of Part B



NOTE: Part B will be initiated only after review of the Part A interim analysis (after 10 subjects have completed Part A).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

It is anticipated that up to 18 subjects will be enrolled in Part A at up to 4 study centers. All of the following inclusion and exclusion criteria will be applied during screening for Part A, with some of the criteria applied during screening for Part B, as indicated.

8.1. Subject Inclusion Criteria

Subjects must meet the following inclusion criteria for enrollment in the study:

1. Subject has signed an informed consent form (ICF) before any study-specific procedures are performed.
2. Subject is between 40 and 75 years of age, inclusive.
3. Subject has a diagnosis of idiopathic PD based on modified UK Brain Bank Criteria (modified to allow individuals with a family history of PD) (Hughes 1992; Appendix 1).
4. Subjects with PD with a duration of less than 7 years and must meet the criteria for Hoehn and Yahr stage 2 or stage 3 (Appendix 2).
5. Subject has a stable dose of antiparkinsonian agents including immediate-release oral Levodopa or Carbidopa-Levodopa (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.
6. Subject is willing to discontinue his/her treatment with immediate-release oral Levodopa or Carbidopa-Levodopa for at least 8 hours prior to dosing with SAGE-217. (Part B also)
7. Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) or amantadine at least 5 days prior to the day of admission (Day -1). (Part B also)
8. Subjects taking an antidepressant drug, sleep medication, or neuroleptic must have been on a stable dose for at least 1 month prior to the baseline visit.
9. Subjects must have a MoCA score of >22.
10. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests. (Part B also)
11. Female subjects must agree to practice a highly effective method of birth control while on study through completion of the last follow-up visit. If a subject discontinues early after receiving a dose of SAGE-217, then the subject must continue this method of birth control for at least 7 days following the last dose of study drug. Highly effective methods of birth control include combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, or sexual abstinence. (Part B also)
12. Male subjects must agree to practice a highly effective method of birth control while on study, and for 13 weeks after receiving the last dose of study drug. Effective methods of

birth control include sexual abstinence, vasectomy, or a condom with spermicide (men) in combination with their partner's highly effective method. (Part B also)

13. Males must be willing to abstain from sperm donation and females from donating eggs while on study through 13 weeks after receiving the last dose of study drug. (Part B also)

8.2. Subject Exclusion Criteria

Subjects who met any of the following exclusion criteria will be excluded from the study:

1. Subjects with a known hypersensitivity to SAGE-217 Oral Solution or its major excipient, HPβCD. (Part B also)
2. Subjects with early PD (Hoehn and Yahr stage 1) or advanced PD (Hoehn and Yahr stage 4 or stage 5).
3. Subjects with any medical or psychiatric condition that jeopardizes/compromises his/her ability for participation. This includes schizophrenia spectrum and other psychotic disorders, substance-related and addictive disorders, feeding and eating disorders, bipolar and related disorders, structural brain disease including but not limited to history of encephalitis or hydrocephalus and history of clinically significant stroke, or anticipating starting psychotherapy or behavior therapy during the course of the study, or who started psychotherapy or behavior therapy within 30 days prior to Part A Day 1.
4. Subjects with a history of:
    a. Electroconvulsive therapy;
    b. Stereotaxic brain surgery (deep brain stimulation) for PD;
    c. History of suicide attempt within 2 years, or has answered YES to questions 3, 4, or 5 on the C-SSRS at the screening or Day -1 visits, or has current suicidal ideation; or
    d. Impulse control disorder.
5. Subjects with severe depression as defined by a BDI-II score >19.
6. Subjects with Type I or Type II diabetes mellitus.
7. Subjects with presence of drug-induced parkinsonism (eg, metoclopramide, flunarizine), metabolic identified neurogenetic disorders (eg, Wilson's disease), encephalitis, or other atypical Parkinsonian syndromes (eg, progressive supranuclear palsy, multiple system atrophy). (Part B also)
8. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease. (Part B also)
9. Subject has clinically significant abnormal physical examination OR 12-lead ECG at the screening or admission visits. NOTE: QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study. ECG may be repeated once if initial values obtained are outside the specified limits. (Part B also)

10. Subject has a history, presence and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies 1 and 2.
11. Subject has exposure to another investigational medication or device within the prior 30 days.
12. Subject has donated one or more units of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing (1 unit = 450 mL). (Part B also)
13. Subject is unwilling or unable to comply with study procedures. (Part B also)
14. Subject has used any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug. (Part B also)

8.3. Entrance Criteria for Part B

In addition to the inclusion and exclusion criteria determined at screening for Part B indicated in Section 8.1 and Section 8.2, respectively, subjects must be able to tolerate at least 10 mg of SAGE-217 in Part A in order to be enrolled into Part B. Part B will not be initiated until results of the Part A interim analysis have been reviewed.

8.4. Subject Withdrawal Criteria

Participation in the study is strictly voluntary. Subjects are free to discontinue the study at any time without giving their reason(s).

A subject must be withdrawn from the study treatment in the event of any of the following:

- Withdrawal of the subject's consent;
- New onset of a condition that would have met exclusion criterion, is clinically relevant and affects the subject's safety, and discontinuation is considered necessary by the Investigators and/Sponsor;
- Occurrence of intolerable adverse events;
- Occurrence of pregnancy;
- Intake of nonpermitted concomitant medication;
- Subject noncompliance;
- Significant protocol deviation determined in consultation with the Medical Monitor.

If a subject fails to attend scheduled assessments during the course of the study, the Investigators must determine the reasons and the circumstances as completely and accurately as possible and document this in the subject's source documents.

Subjects may be withdrawn from the study if there is concern for the subject's safety or it is determined that the subject is no longer a qualified participant. Any subject who is withdrawn from the study for any reason is to have the final visit assessments performed.

Subjects who withdraw or are withdrawn from the study may be replaced.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol.

9.1.1. Part A

Subjects participating in Part A of the study will take study drug (SAGE-217) in an open-label manner. 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 the following 3 days (Days 1 to 3). On the morning of Day 4, subjects will stop their immediate-release oral Levodopa and take SAGE-217 for 4 days (Days 4 to 7) in the AM with food. On Day 4, subjects will receive a 30 mg dose of SAGE-217. Subjects not tolerating 30 mg will receive 20 mg the next day, and subjects not tolerating 20 mg will receive 10 mg the next day. The dose received on Day 7 will be defined as the tolerated dose for that subject, with this dose to be used as the starting dose for Part B for that subject.

Subjects not tolerating 10 mg will not be able to continue in the study and may be replaced. Levodopa treatment will be resumed on Day 8 and continue through Day 14.

9.1.2. Part B

In order to qualify for Part B of the study, a subject must tolerate a dose of at least 10 mg of SAGE-217 Oral Solution. On Day 1 of Part B, subjects will be randomized in a 1:1 manner to open-label Levodopa plus blinded SAGE-217 Oral Solution or placebo.

- Subjects randomized to the Levodopa plus placebo arm will receive Levodopa plus SAGE-217 placebo oral solution in the AM for the first 4 days (Days 1 to 4).
- Subjects randomized to the Levodopa plus SAGE-217 Oral Solution arm will receive this combination in the AM for the first 4 days (Days 1 to 4). Subjects will receive their individually established tolerated dose of SAGE-217 Oral Solution from Part A.
- 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.

9.2. Concomitant Medications

9.2.1. Prior/Concomitant Medications

Any concomitant medication determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study under the guidance outlined in Section 9.2.

Record the name, start date (if known), indication for use and whether ongoing or stopped of medications/treatments taken within 2 weeks prior to study entry as well as any medications taken during the study.

The charts of all study participants will be reviewed for new concomitant medications through discharge from the unit. Chart reviews will include examination of nursing and physician progress notes, vital signs, and medication records in order to identify adverse events that may be associated with new concomitant medications. New concomitant medications, ongoing concomitant medications with a change in dose, and medical procedures ordered (eg, laboratory assessments, computed tomography or magnetic resonance imaging scans) will be reviewed to determine if they are associated with an adverse event not previously identified.

The Investigator will document all doses of Levodopa and Carbidopa-Levodopa taken by the subject and the use of rescue medication.

9.2.2. Prohibited Medications

Subjects who have used any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug are to be excluded from the study; these medications/products are prohibited during the study.

The anticholinergic drug classes listed in Appendix 3 and amantadine are not permitted in the 5 days prior to the admission visit (Day -1) of each part of the study. The list provides non-exhaustive examples of each drug class.

9.3. Treatment Compliance

Study drug (SAGE-217 or matched placebo) will be prepared by the site pharmacist. All doses of study drug will be administered by site staff while the subject is confined to the clinical unit. The Investigator(s) or designee will record the time and dose of study drug administration in the source documents. Any reasons for noncompliance will also be documented, including:

- Missing visits;
- Interruptions in the schedule of administration; and
- Nonpermitted medications.

The time at which study procedures are conducted should follow the protocol timelines as closely as possible.

9.4. Randomization and Blinding

Part A of the study is open-label.

In 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 groups: open-label Levodopa plus blinded SAGE-217 Oral Solution or placebo oral solution. Subjects, clinicians, and the study team will be blinded to treatment allocation. The pharmacist, who will prepare the oral solutions 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.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dosages. The 6 mg/mL stock SAGE-217 Oral Solution will be compounded from SAGE-217 Drug Substance Powder in the Bottle and Excipient(s) in the Bottle (manufactured under current Good Manufacturing Practice [GMP] conditions [redacted]) and further admixed at the clinical site in preparation for dosing. Placebo will be matched to SAGE-217 study drug. Detailed instructions for study drug preparation will be provided in the Pharmacy Manual.

The Sponsor will not provide Levodopa or Carbidopa-Levodopa during the study; subjects will use their prescribed Levodopa or Carbidopa-Levodopa.

10.2. Study Drug Packaging and Labeling

The composition and pharmaceutical quality of the investigational product will be maintained according to the current GMP and Good Clinical Practice (GCP) guidelines and available for review in the study medication documentation. Study drug will be provided to the site as powder in the bottle and excipient(s) in the bottle units to be compounded in the pharmacy at a volume of 125 mL of a 6 mg/mL stock solution and then further diluted to approximately 40 mL at the identified doses. Study drug labels with all required information and conforming to all applicable Code of Federal Regulations and GMP/GCP guidelines will be prepared by the clinical research organization.

10.3. Study Drug Storage

Upon receipt of study drug (SAGE-217 Oral Solution and placebo oral solution), the Investigator or designee will inspect the materials and complete and return the acknowledgment of receipt form enclosed with the parcel. A copy of the signed receipt will be kept in the study files.

The study drug materials for SAGE-217 Oral Solution and placebo oral solution must be carefully stored at the temperature specified in the Pharmacy Manual (eg, clinical dosing solutions stored at approximately 2 to 8°C for 11 days with 24 hours of room temperature excursions allowed after preparation), safely and separately from other drugs. The study drug may not be used for any purpose other than the present study. After the study is completed, all unused study drug must be retained, returned as directed, or destroyed on site per the Sponsor's instructions.

The Investigator or designee will be responsible for ensuring appropriate storage, compounding, dispensing, inventory, and accountability of all clinical supplies. An accurate, timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory must be available for inspection by the designated representatives of the Sponsor or the Sponsor's representatives on request, and must include the information below:

- The identification of the subject to whom the drug was dispensed;
- The date(s) and quantity of the drug dispensed to the subject; and

- The product lot/batch number.

The preparation of the study drugs must be documented on a 'Drug Preparation and Dispensing Log Form' or similar form.

A copy of the inventory record and a record of any clinical supplies that have been destroyed must be documented. This documentation must include at least the information below or as agreed with the Sponsor:

- The number of prepared units;
- The number of administered units;
- The number of unused units;
- The number of units destroyed at the end of the study;
- The date, method, and location of destruction.

10.4. Study Drug Preparation

Each bottle of SAGE-217 Oral Solution 6 mg/mL will be compounded at the clinical pharmacy from components manufactured [redacted] and supplied by the Sponsor per the directions provided in the Pharmacy Manual. The batch formula for a 125 mL solution of the 6 mg/mL stock solution is shown in Table 5.

Table 5: Batch Formula for 125 mL of Stock SAGE-217 Oral Solution 6 mg/mL

Ingredient	Compendia Specification	Concentration (mg/mL)	Amount (mg/Bottle)
SAGE-217	not applicable	6	750
HPβCD [redacted]	USP/EP	457	57,100
Sucralose	USP/NF	0.025	3.124
Water for Injection	USP	not applicable	85,650

Abbreviations: EP = European Pharmacopeia; HPβCD = hydroxypropyl-β-cyclodextrin; NF = National Formulary; USP = United States Pharmacopeia

Additional excipients may be utilized in placebo to match the taste of SAGE-217 Oral Solution. They include sucrose octaacetate, tannic acid, and ammonium glycyrrhizate. The quantities may vary depending on the dose of SAGE-217.

10.5. Administration

SAGE-217 Oral Solution or placebo oral solution will be administered in the morning with food.

Doses of SAGE-217 and placebo for SAGE-217 will be prepared as an approximate 40 mL oral solution to be swallowed all at once, followed by approximately 200 mL of water that has been used to rinse the dosing bottle. The start time of swallowing the approximately 40 mL oral solution is time zero for all assessments. Subjects may have assistance from the clinic staff when taking the study drug.

During Confinement, each subject's antiparkinsonian agents, including Levodopa or Carbidopa-Levodopa, will be administered by site personnel according to the site's standard operating procedures.

10.6. Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator or designee must maintain a record of all study drug received, used, and discarded. It must be clear from the records which subject received which dose of active or placebo treatment.

The Sponsor will be permitted access to the study supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation. Only unblinded personnel will be able to access the study drug and accountability documentation from first dosing through database hard lock.

The Investigator will document all doses of Levodopa or Carbidopa-Levodopa taken by the subject, including rescue doses.

10.7. Study Drug Handling and Disposal

The pharmacist or designee for drug accountability is to document the date and time of initial compounding, subsequent admixture of dosing solutions, administration of study drug, and for which subject the study drug was intended (ie, record subject initials and birth date or other unique identifier).

At the end of the study, any unused study drug will be retained or returned to the Sponsor for destruction or destroyed locally per the Sponsor's directions; disposition of study drug will be documented.

11. ASSESSMENT OF EFFICACY

Efficacy assessments include evaluation of PD symptoms by the MDS-UPDRS, [redacted] Assessments will be performed periodically during the study as outlined in the Schedule of Events (Table 2 and Table 3, respectively.

11.1. Movement Disorder Society – Unified Parkinson's Disease Rating Scale

The UPDRS is the most commonly used scale in clinical studies of PD (Ramaker 2002). In 2007, the MDS revised the scale, which was known as the MDS-UPDRS (Goetz 2007), and subsequently demonstrated the validity of the MDS-UPDRS for rating PD (Goetz 2008). The modified UPDRS includes four scales, with various subscales. Each item is rated from 0 (normal) to 4 (severe) (Table 6). 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)

Table 6: Rating 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

Several questions in Part I and all questions in Part II can be answered by the patient/caregiver and completed without the Investigator's input. The remaining questions in Part I that deal with complex behaviors, the objective assessments of parkinsonism (Part III), and the questions that deal with motor fluctuations and dyskinesias (Part IV) are completed by Investigator interview. The time required for administering the MDS-UPDRS is estimated to be less than 10 minutes for the interview items of Part I, 15 minutes for Part III, and 5 minutes for Part IV (Goetz 2008). The complete MDS-UPDRS is to be administered in Part A at screening, Admission (Day -1), on Day 8 prior to resuming Levodopa, and on Day 14. The complete MDS-UPDRS is to be administered in Part B at screening, Admission (Day -1), on Day 9 prior to resuming Levodopa; and on Days 15 and 22. In both Parts A and B, the Admission (Day -1) complete MDS-UPDRS is performed only if the time between Screening and Admission is ≥7 days; otherwise, the MDS-UPDRS Part III only is performed.

Part III of the MDS-UPDRS 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, global spontaneity of movement (Goetz. 2008). Part III of the MDS-UPDRS (motor examination) is to be completed in Part A at 2, 4, 8, and 12 hours postdose on Days 1, 2, 3, 4, 5, 6, and 7, and in Part B at 2, 3, 4, 8, and 12 hours postdose on Days 1, 2, 3, 4, 5, 6, 7, and 9. If the complete MDS-UPDRS is not performed on Admission due to Admission taking place <7 days after Screening, then Part III only should also take place on Admission (Day -1) for both Parts A and B. MDS-UPDRS is to be assessed within ±10 minutes of the scheduled times through the 4-hour time point and within ±15 minutes of the scheduled times for the 6-hour through 12-hour time points. The MDS-UPDRS is provided in Appendix 4.

11.2. Exploratory Endpoints

[redacted]

[redacted]

[redacted]

12. PHARMACOKINETICS

12.1. Blood Sample Collection

In Part A, plasma samples for PK analysis will be collected predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Day 4; predose on Day 5 and Day 6; predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Day 7; in AM of Day 8; and Day 14. In Part B, plasma samples for PK analysis will be collected predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Days 1 to 4; 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 the AM on Day 9; and on Days 15 and 22. The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. Samples are to be collected within ±5 minutes of the scheduled sampling time. The Investigator or designee will arrange to have the plasma samples processed, stored, and transported as directed for bioanalysis.

An additional PK sample may be collected at any time if clinically indicated and at the discretion of the Investigator (eg, for unusual or severe adverse events).

Each sample will be marked with unique identifiers such as the study number, subject number, and the nominal sample time. The date and actual time that the blood sample was taken will be recorded on the eCRF or electronically with a bar code or other method.

12.2. Storage and Shipment of Pharmacokinetic Samples

The plasma samples should be kept frozen at approximately -70 to -80°C until analyzed. They should be packed as directed to avoid breakage during transit and with sufficient dry ice to prevent thawing for at least 72 hours. A specimen-identification form must be completed and sent to the laboratory with each set of samples. The clinical site will arrange to have the plasma samples transported as directed for bioanalysis as detailed in the PK instructions.

12.3. Sample Analysis

Bioanalysis of plasma samples for the determination of concentrations of SAGE-217 and possibly SAGE-217 metabolites will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory. Pharmacokinetic parameters will be derived such as area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), the distributional half-life and terminal half-life ($t_{1/2}$), and steady-state drug concentration in the plasma (C_{ss}).

13. ASSESSMENT OF SAFETY

13.1. Safety and Tolerability Parameters

Safety and tolerability of study drug will be evaluated by adverse event reporting, vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, and SSS and MOAA/S scores.

13.1.1. Demographic/Medical History

Age, gender, race, and ethnic origin will be recorded at the Screening visit for Part A. A full medical history, including PD history (eg, time of diagnosis, staging) and medication history, will be recorded at the Screening visit for Part A and updated, as needed, as screening for Part B.

13.1.2. Vital Signs

Vital signs comprise respiratory rate, temperature, and supine (supine for at least 5 minutes prior to the measurement) and standing systolic and diastolic blood pressure and heart rate.

In Part A, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in AM of Day 8; and on Day 14. In Part B, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 8; in AM on Day 9; and on Days 15 and 22. Vital signs and pulse oximetry are to be assessed within ±10 minutes of the scheduled times through the 4-hour time point and within ±15 minutes of the scheduled times for the 6-hour through 16-hour time points.

13.1.3. Weight and Height

Body weight and height will be measured at the Screening visits for Parts A and B.

13.1.4. Physical Examination

A physical examination of all major body systems will be undertaken and recorded at the Screening visits for Parts A and B. Symptom-directed physical examinations will be performed during Part A on Admission (Day -1), Day 1, Day 3, Day 4, Day 6, and Day 8. Symptom-directed physical examinations will be performed during Part B on Admission (Day -1), Day 1, Day 3, Day 4, Day 5, Day 7, Day 8, Day 9, and Day 15.

13.1.5. Electrocardiogram (ECG)

A supine 12-lead ECG will be performed at the times specified below and the standard intervals recorded as well as any abnormalities.

In Part A, the 12-lead ECG will be assessed at screening and Admission (Day -1); predose on Days 1 and 3; predose and 1 and 12 hours postdose on Days 4, 5, 6, and 7; in AM on Day 8; and Day 14. In Part B, the 12-lead ECG will be assessed at screening and Admission (Day -1); predose and 1 and 12 hours postdose on Days 1 through 8; in AM on Day 9; Days 15 and 22.

All time points are relative to the time of dosing. ECGs are to be performed within ±10 minutes of the predose and 1-hour time points and within ±15 minutes of the 12-hour time point.

13.1.6. Laboratory Assessments

In Part A, blood samples will be collected for hematology and serum chemistry at the Screening visit, on Admission (Day -1), predose on Days 4, 6, and 8; and on Day 14. Urine samples will be collected in Part A at screening and Admission (Day -1); predose on Day 4 and Day 7; and on Day 14. In Part B, blood samples will be collected at screening and Admission (Day -1); predose on Days 1, 3, 4, 5, 6, and 8; on Day 9 and Day 15. Urine samples will be collected in Part B at screening and Admission (Day -1); predose on Day 4 and Day 8; and on Day 15.

Serum and urine samples for pregnancy tests (females only) will also be collected. These assessments should be performed in accordance with the Schedule of Events (Table 2 and Table 3 as outlined individually below.

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS). Screening results considered abnormal, CS recorded at the Screening visit may make the subject ineligible for the study pending review by the Medical Monitor. Clinical laboratory results that are abnormal, CS during the study but within normal range at baseline and/or indicate a worsening from baseline will be considered adverse events, assessed according to Section 13.2, and recorded in the eCRF.

13.1.6.1. Hematology

Hematology tests will include complete blood count (CBC), including red blood cells, white blood cells with differentiation, hemoglobin, hematocrit, reticulocytes, and platelets. The coagulation panel will include activated partial thromboplastin time, prothrombin time, and international normalized ratio.

13.1.6.2. Blood Chemistry

Serum chemistry tests will include serum electrolytes, renal function tests, including creatinine, blood urea nitrogen, bicarbonate or total carbon dioxide, liver function tests, including total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), total protein, and albumin.

13.1.6.3. Urinalysis

Urinalysis will include assessment of protein, blood, glucose, ketones, bile, urobilinogen, hemoglobin, leukocyte esterase, nitrites, color, turbidity, pH, and specific gravity.

13.1.6.4. Virus Serology

Subjects will be screened for hepatitis (HBsAg and anti-HCV) and HIV prior to being enrolled in the study.

13.1.6.5. Pregnancy Screen

Females of childbearing potential will be tested for pregnancy at Parts A and B by serum pregnancy test at the Screening visits and by urine pregnancy test on Day -1 (Admissions).

13.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS)

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

If in the opinion of the Investigator, the subject is showing any suicidal tendency, no further study drug will be administered and the subject will be referred to a psychologist or psychiatrist for further evaluation. This information will be tracked.

The "Baseline/Screening" C-SSRS form will be completed on Screening of Part A (lifetime history and past 24 months). In Part A, the "Since Last Visit" C-SSRS form will be completed on Admission (Day -1); 12 hours postdose on Days 1, 2, and 3; predose on Days 4, 5, 6, and 7; and on Days 8 and 14. In Part B, the "Since Last Visit" C-SSRS form will be completed on Admission (Day -1); 12 hours postdose on Day 1 through Day 8; and on Days 9, 15, and 22. The C SSRS is provided in Appendix 9.

13.1.8. Stanford Sleepiness Scale (SSS)

The SSS is 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'.

In Part A, the SSS will be administered on Admission (Day -1); predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in the AM on Day 8; and Day 14. All time points are relative to the time of dosing. 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. In Part B, the SSS will be administered on Admission (Day -1); predose on Days 1 through 8; in AM on Day 9; and Days 15 and 22. The SSS should be performed prior to the MOAA/S score. The SSS is provided in Appendix 10.

13.1.9. Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S)

The MOAA/S allows exploration of deeper sedation states than the SSS. If an 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. In Part A, the MOAA/S assessment should be conducted after other assessments that are scheduled at the same time point. In Part A, the MOAA/S will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 3, 4, 5, 6, and 7; in AM on Day 8; and Day 14. In Part B, the MOAA/S will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 8; in AM on on Day 9; and Days 15 and 22. The MOAA/S 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 for the 6-hour through 16-hour time points. The MOAA/S is provided in Appendix 11.

13.2. Adverse and Serious Adverse Events

Adverse events will be collected after the ICF has been signed. Medical conditions that occur after the ICF has been signed will be captured on the adverse event eCRF.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (version 18.1 or higher).

13.2.1. Definition of Adverse Events

13.2.1.1. Adverse Event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an adverse event can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All adverse events that occur after any subject has been enrolled, before treatment, during treatment, or following the cessation of treatment until the Day 22 Follow-up visit of Part B, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics.

13.2.1.2. Suspected Adverse Reaction

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

13.2.1.3. Serious Adverse Event

A serious adverse event is an adverse event occurring during any study phase and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- It results in death
- It is immediately life-threatening
- It requires inpatient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- It results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

All serious adverse events that occur after any subject has been enrolled, before treatment, during treatment, and until the Day 22 Follow-up visit of Part B, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics.

13.2.1.4. Recording Sedation as an Adverse Event

Sedation will be assessed using protocol-specified rating scales. In order to standardize the reporting of sedation as adverse events, Investigators must record sedation as an adverse event if there is a score of >5 on the SSS and/or a score of ≤2 on the MOAA/S. Consideration should be given to the most appropriate term to describe the sedation characteristics.

13.2.2. Pregnancy

Any pregnancy occurring during this study will be reported within 24 hours of notification of the Investigator. The Investigator will promptly notify the Medical Monitor and withdraw the subject from the study. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The Investigator should request permission to contact the subject, the subject's spouse/partner (if the subject is male and his spouse/partner becomes pregnant) or the obstetrician for information about the outcome of the pregnancy (spontaneous miscarriage, elective termination, live birth), and in the case of a live birth, about any congenital abnormalities. If a congenital abnormality is reported, then it should be recorded in the source documents and reported as a serious adverse event. Spontaneous miscarriages should also be reported and handled as serious adverse events. Elective abortions without complications should not be handled as adverse events.

13.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each adverse event (unrelated, possibly related or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the adverse event should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the adverse event, then the adverse event should be considered "related."

Not related	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possibly related	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.
Probably related	The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.

If the relationship between the adverse event/serious adverse event and the investigational product is determined to be "possible" or "probable", the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

13.4. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as adverse events unless they prompt corrective medical action by the Investigator, constitute a serious adverse event or lead to discontinuation of administration of study drug.

Information about adverse events will be collected from the signing of the ICF until the final visit of the study for that subject. Adverse events that occur after the first administration of study drug will be denoted TEAEs.

All adverse events will be followed until they are resolved or have reached a clinical plateau with no expectation of future change.

The adverse event term should be reported in standard medical terminology when possible. For each adverse event, the Investigator will evaluate and report the onset (date and time), resolution or clinical plateau (date and time), intensity, causality, action taken, outcome, and whether or not it caused the subject to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe adverse events. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.2.1.3. An adverse event of severe intensity may not be considered serious.

13.5. Reporting Serious Adverse Events

All serious adverse events (regardless of causality) will be recorded from the signing of the ICF until the Day 22 Follow-up visit of Part B. Any serious adverse events considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All serious adverse events must be reported to the Sponsor or Sponsor's designee immediately by phone and in writing within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the serious adverse event pages, verify the accuracy of the information recorded on the serious adverse event pages with the corresponding source documents, and send a copy to Sage Therapeutics or designee.

Additional follow-up information, if required or available, should be sent to Sage Therapeutics or designee within 24 hours of receipt; a follow-up serious adverse event form should be completed and placed with the original serious adverse event information and kept with the appropriate section of the CRF and/or study file.

Sage Therapeutics or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB of all serious adverse events that occur at his or her site if applicable per the IRB's requirements. Investigators

will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB of these additional serious adverse events.

14. STATISTICAL METHODS AND CONSIDERATIONS

14.1. Data Analysis Sets

The safety population is defined as all subjects who are administered study drug.

The efficacy population will consist of all subjects in the safety population who receive at least one dose of study drug and have at least one postdose MDS-UPDRS evaluation.

The PK population will consist of all subjects in the safety population with sufficient plasma concentrations for PK evaluations.

Separate populations will be defined for each part of the study.

14.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. No imputation process will be used to estimate missing data. No sensitivity analysis of missing data will be performed.

14.3. Demographics and Baseline Characteristics

Demographics, such as age, gender, race, and ethnicity, and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized.

Categorical summaries, such as gender and race, will be summarized by frequency and percentage. Continuous summaries, such as age, height, weight, BMI, and baseline vital signs, will be summarized using descriptive statistics.

Hepatitis, 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 by subject.

14.4. Efficacy Endpoints

The primary endpoints of this study relate to safety and tolerability. Efficacy assessments include evaluation of PD symptoms by the MDS-UPDRS, [redacted]

14.4.1. Secondary Efficacy Endpoints

In Part A, changes in the MDS-UPDRS – Part III score will be summarized overall and by tolerated dose. In Part B, changes in the MDS-UPDRS – Part III score and the MDS-UPDRS – Parts I-IV total score will be summarized overall and by randomized treatment sequence and tolerated dose.

14.4.2. Exploratory Efficacy Endpoints

[redacted]

[redacted]

14.5. Safety and Tolerability Analyses

Data from vital signs, clinical laboratory measures, ECG, C-SSRS, SSS, and MOAA/S will be summarized using descriptive statistics by group and time point, where applicable. Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and will be summarized using descriptive statistics. Out-of-range safety endpoints may be categorized as low or high, where applicable. For all categorical endpoints, summaries will include counts and percentages.

14.5.1. Adverse Events

Adverse events will be coded using the MedDRA coding system (version 18.1 or higher). The analysis of adverse events will be based on the concept of TEAEs. A TEAE is defined as an adverse event with onset after the start of open-label study drug, or any worsening of a pre-existing medical condition/adverse event with onset after the start of open-label study drug and until 14 days after the last dose. The incidence of TEAEs will be summarized overall and by MedDRA System Organ Class, preferred term, and dose group. Incidences will be presented in order of decreasing frequency. In addition, summaries will be provided by maximum severity (see Section 13.4) and relationship to study drug (see Section 13.3).

Treatment-emergent adverse events leading to discontinuation and serious adverse events (see Section 13.2.1.3 for definition) with onset after the first dose of open-label study drug will also be summarized.

All adverse events and serious adverse events (including those with onset or worsening before the start of open-label study drug) through the Day 22 Follow-up visit of Part B will be listed.

14.5.2. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from baseline of Part A and Part B in vital signs will be evaluated by time point.

14.5.3. Physical Examinations

Screening physical examination results for Part A and Part B will be listed by subject. Any clinically significant physical examination will be recorded in medical history. Physical examination findings will be listed by subject and visit; abnormal findings will be flagged on the listing.

14.5.4. 12-Lead ECG

The following ECG parameters will be listed for each subject: heart rate, PR, QRS, QT, QTc, and QTcF. Any clinically significant abnormalities or changes in ECGs should be listed as an adverse event. Electrocardiogram findings will be listed by subject and visit.

14.5.5. Clinical Laboratory Evaluations

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline of Parts A and B in clinical laboratory measures will be summarized.

14.5.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality data collected on the C-SSRS will be listed for all subjects. Listings will include behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

14.5.7. Stanford Sleepiness Scale (SSS)

Sedation data collected on the SSS will be listed for all subjects. Changes in score over time will be represented graphically, and change from baseline of Part A and Part B will be summarized.

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

Sedation data collected on the MOAA/S will be listed for all subjects. Changes in score over time will be represented graphically, and change from baseline of Part A and Part B will be summarized.

14.5.9. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and will be coded using World Health Organization (WHO)-Drug dictionary September 2015, or later.

Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those taken during the 4 weeks prior to the date of the first dose of open-label study drug. Concomitant medications are defined as those with a start date on or after the first dose of open-label study drug, or those 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. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Concomitant medications will be assigned to the study part in which they are being taken. 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.

The use of rescue medication will be recorded and summarized.

14.6. Pharmacokinetic Analysis

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics. Time to reach maximum concentration (t_{max}) will be summarized using number (n), mean, standard deviation, median, minimum, and maximum. All other PK parameters will be summarized using n, geometric mean, coefficient of variation, median, minimum, and maximum and listed by subject.

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

[redacted] Additional exposure-response analyses may be performed for other measures of efficacy and safety.

14.7. Determination of Sample Size

Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14. Approximately 12 subjects are anticipated to be randomized to 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.

14.8. Changes From Protocol Specified Analyses

Any changes from the analytical methods outlined in the protocol will be documented in the final statistical analysis plan.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of <Sponsor> will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sage Therapeutics or designee or its representatives. This will be documented in a Clinical Study Agreement between Sage Therapeutics and the Investigator.

During the study, a monitor from Sage Therapeutics or designee will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s);
- Confirm that facilities remain acceptable;
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts);
- Record and report any protocol deviations not previously sent to Sage Therapeutics or designee; and
- Confirm adverse events and serious adverse events have been properly documented on eCRFs and confirm any serious adverse events have been forwarded to Sage Therapeutics or designee and those serious adverse events that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

15.2. Audits and Inspections

Authorized representatives of Sage Therapeutics, a regulatory authority, an Independent Ethics Committee (IEC) or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sage Therapeutics or designee audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Council on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency about an inspection.

15.3. Institutional Review Board (IRB)

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator and institution will permit study-related monitoring, audits, IRB review, and regulatory inspections as requested by Food and Drug Administration, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (ie, original medical records, laboratory reports, hospital documents, progress reports, signed ICFs) in addition to eCRFs.

Quality assurance and quality-control systems with written standard operating procedures will be followed to ensure this study will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality-assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements made by the Sponsor with the Investigator/institution and any other parties involved with the clinical study will be in writing in a separate agreement.

17. ETHICS

17.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Sage Therapeutics or designee before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Sage Therapeutics or designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

17.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and the most recent amendment (2008) and are consistent with ICH/GCP and other applicable regulatory requirements.

17.3. Written Informed Consent

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject’s signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

18. DATA HANDLING AND RECORDKEEPING

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

Electronic case report forms will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, and subject status.

The Investigator will have access to the electronic data capture system and will receive a copy of the subject eCRF data at the end of the study. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

18.1. Inspection of Records

Sage Therapeutics or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

18.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Sage Therapeutics or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18.3. Confidentiality

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available study registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used

towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

19. PUBLICATION POLICY

All information concerning SAGE-217 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

20. LIST OF REFERENCES

Belelli D, Casula A, Ling A, Lambert JJ. The influence of subunit composition on the interaction of neurosteroids with GABA(A) receptors. Neuropharmacology. 2002 Sep;43(4):651- 61.

[redacted]

Bergman H, Deuschl G. Pathophysiology of Parkinson's disease: from clinical neurology to basic neuroscience and back. Mov Disord. 2002;17:S28-S40.

[redacted]

di Michele F, Longone P, Romeo E, et al. Decreased plasma and cerebrospinal fluid content of neuroactive steroids in Parkinson's disease. Neurol Sci. 2003;24(3):172-3.

Goetz CG, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. Mov Disord. 2007;22(1):41–4.

Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov Disord. 2008;23(15):2129–70.

Hoehn M, Yahr M. Parkinsonism: onset, progression and mortality. Neurology. 1967;17(5):427-42.

[redacted]

Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP. 1992;55:181-4.

Jankovic J. Motor fluctuations and dyskinesia in Parkinson's disease: Clinical manifestations. Mov Disord. 2005;11:11-6.

Jankovic J. Parkinson's' disease: clinical features and diagnosis. JNNP. 2008;79:368-76.

Kasten M, Bruggemann N, Schmidt A, Klein C. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology. 2010;75 (5):478–9.

[redacted]

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.

Ramaker C, Marinus J, Stiggelbout AM, et al. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. Mov Disord. 2002;17(5):867–76.

Siderowf A, Lang AE. Pre-motor Parkinson's disease; concepts and definitions. Mov. Disord 2012;27, 608-16.

Stern MB. Dopamine agonists modify the course of Parkinson disease. Arch Neurol. 2004;61:1969-71.

Weiner WJ. Initial treatment of Parkinson disease: levodopa or dopamine agonists. Arch Neurol. 2004;61:1966-9.

Winkler C, Bentlage C, Nikkhah G, et al. Intracranial transplants of GABA-rich striatal tissue induce behavioral recovery in the rat Parkinson model and promote the effects obtained by intrastriatal dopaminergic transplants. Exp. Neurol. 1999;155:165-186.

21. APPENDICES

Copies of scales and questionnaires included in the following appendices are for reference only; the rating scales and questionnaires reproduced in the eCRFs are to be used for actual subject assessment per the Schedule of Events.

APPENDIX 1. UNITED KINGDOM BRAIN BANK CRITERIA

UK PARKINSON'S DISEASE SOCIETY BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA*

Step 1. Diagnosis of Parkinsonian Syndrome

- Bradykinesia
- At least one of the following
  - Muscular rigidity
  - 4-6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease

- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

**From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181-184.*

APPENDIX 2. HOEHN AND YAHR STAGING CRITERIA

The Hoehn and Yahr scale, a commonly used system for describing how the symptoms of Parkinson's disease progress, was first published in 1967 (Hoehn 1967). The original scale included 5 disease stages, numbered 1 to 5.

Original Hoehn and Yahr Scale

Stage 1	Unilateral involvement only, usually with minimal or no functional disability
Stage 2	Bilateral or midline involvement without impairment of balance
Stage 3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent
Stage 4	Severely disabling disease; still able to walk or stand unassisted
Stage 5	Confinement to bed or wheelchair unless aided

APPENDIX 3. ANTICHOLINERGIC DRUGS

The following drugs are not permitted in the 5 days prior to receiving the first dose of study drug in Part A and Part B. The list below gives a non-exhaustive list of examples of each drug class.

A. Antimuscarinic agents

Atropine	Benzatropine	Biperiden	Chlorpheniramine
Dicyclomine	Dimenhydrinate	Diphenhydramine	Doxepin
Doxylamine	Glycopyrrolate	Hydroxyzine	Ipratropium
Orphenadrine	Oxitropium	Oxybutynin	Tolterodine
Tiotropium	Trihexyphenidyl	Scopolamine	Solifenacin
Tropicamide			

Tricyclic antidepressants (amitriptyline, clomipramine, doxepin, imipramine, trimipramine, amoxapine, desipramine, nortriptyline, protriptyline)

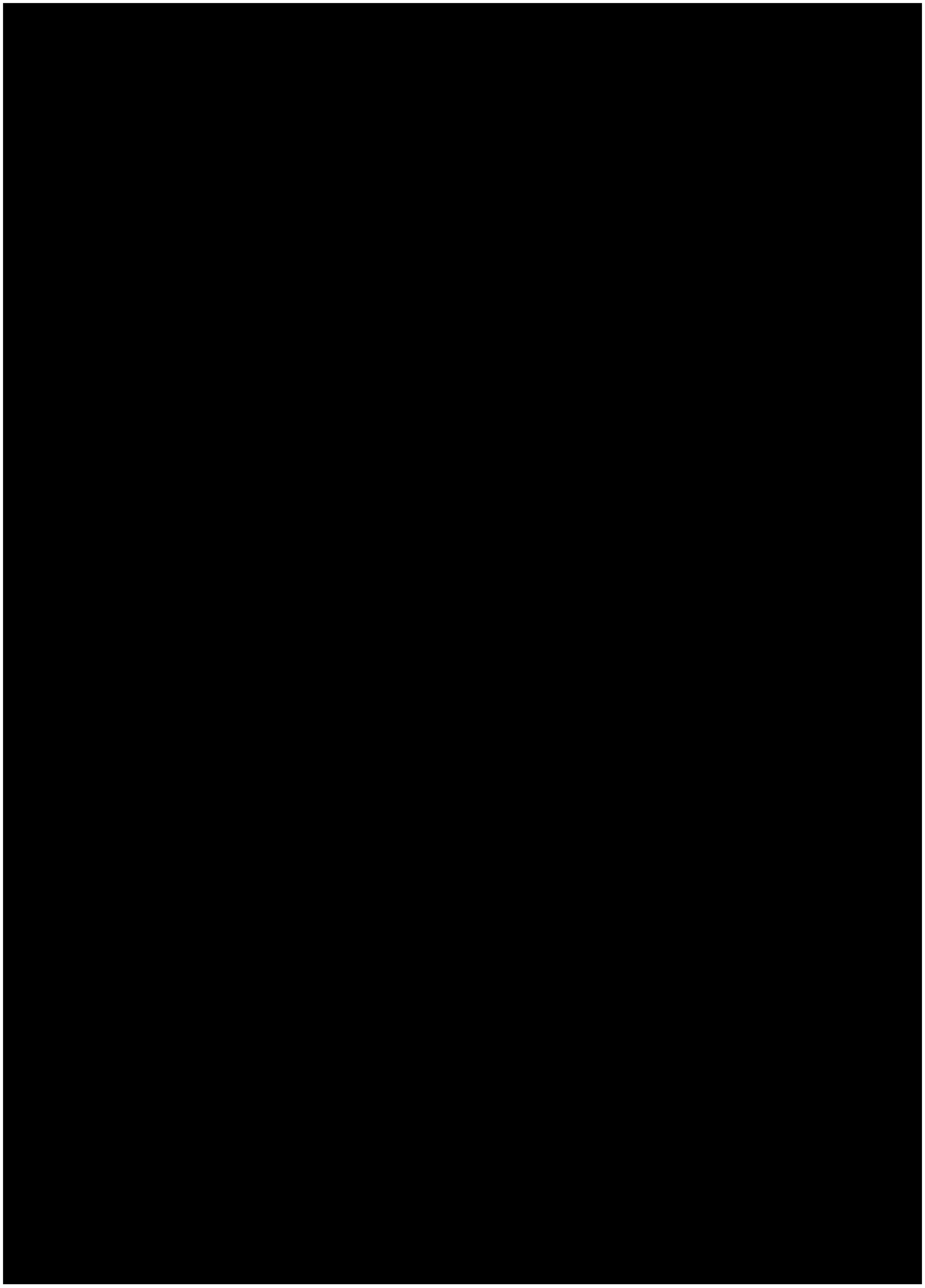
B. Antinicotinic agents:

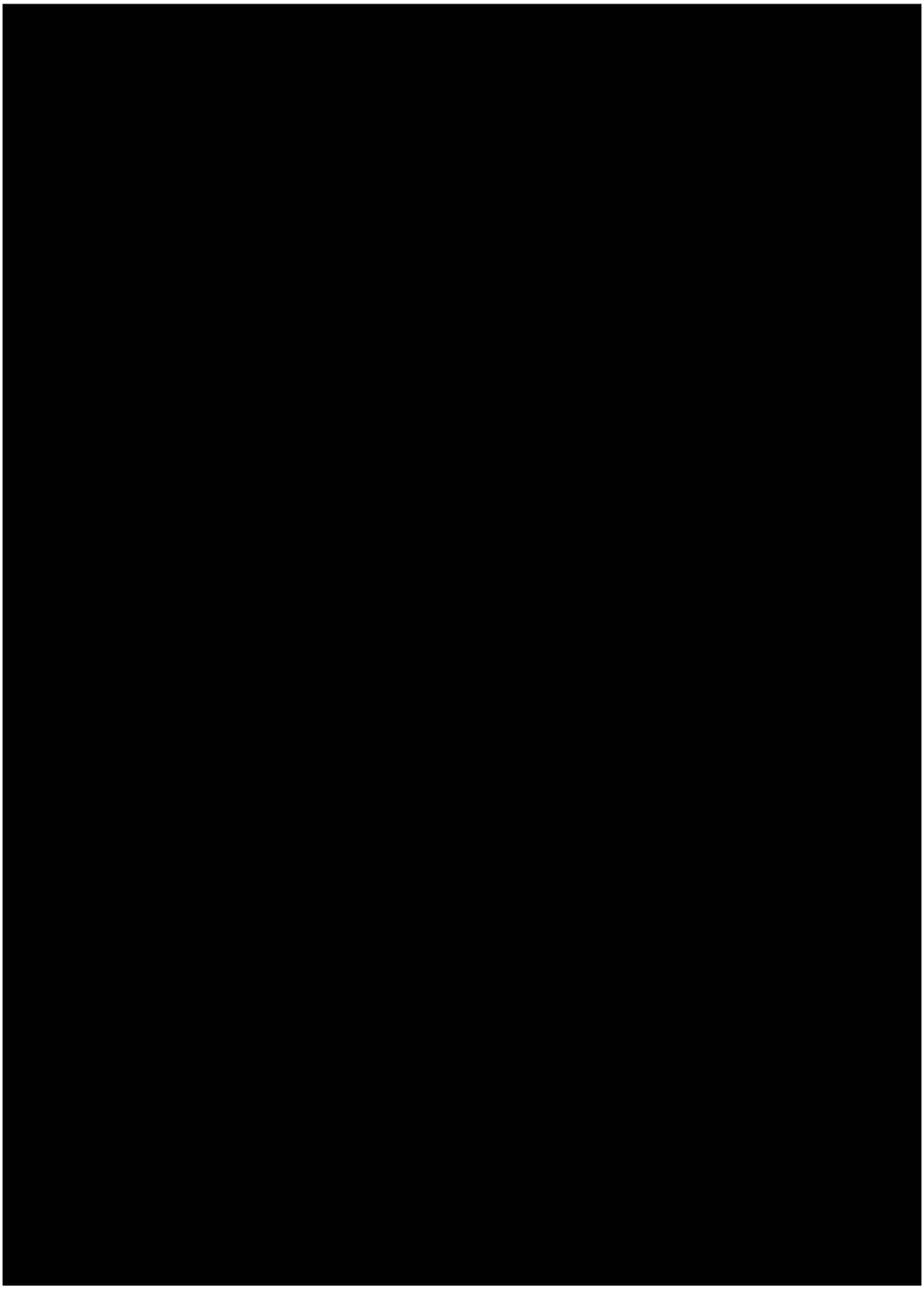
Bupropion	Dextromethorphan	Doxacurium	Hexamethonium
Mecamylamine	Tubocurarine		

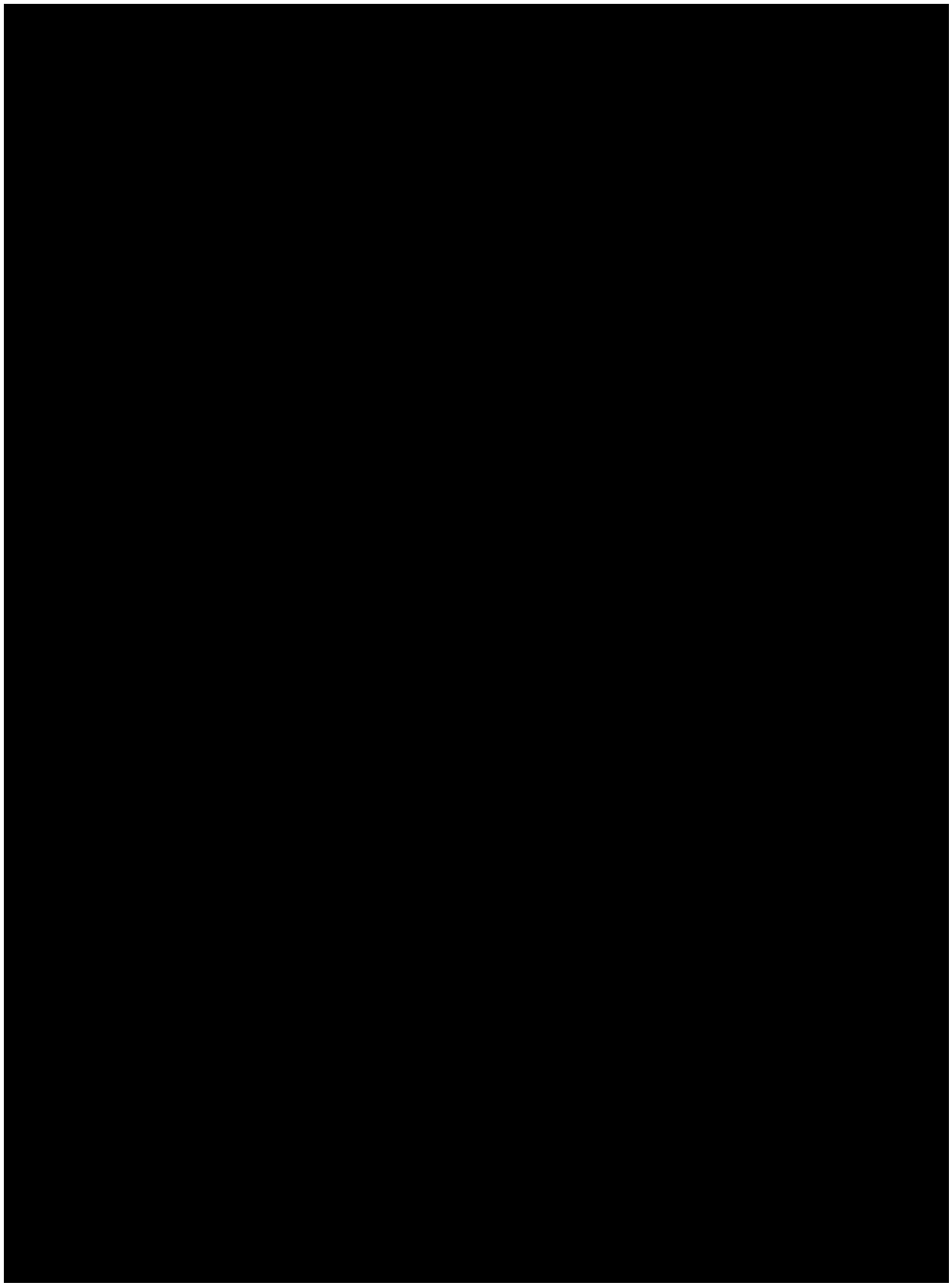
APPENDIX 4. MOVEMENT DISORDER SOCIETY-UNIFIED PARKINSON'S DISEASE RATING SCALE (MDS-UPDRS)

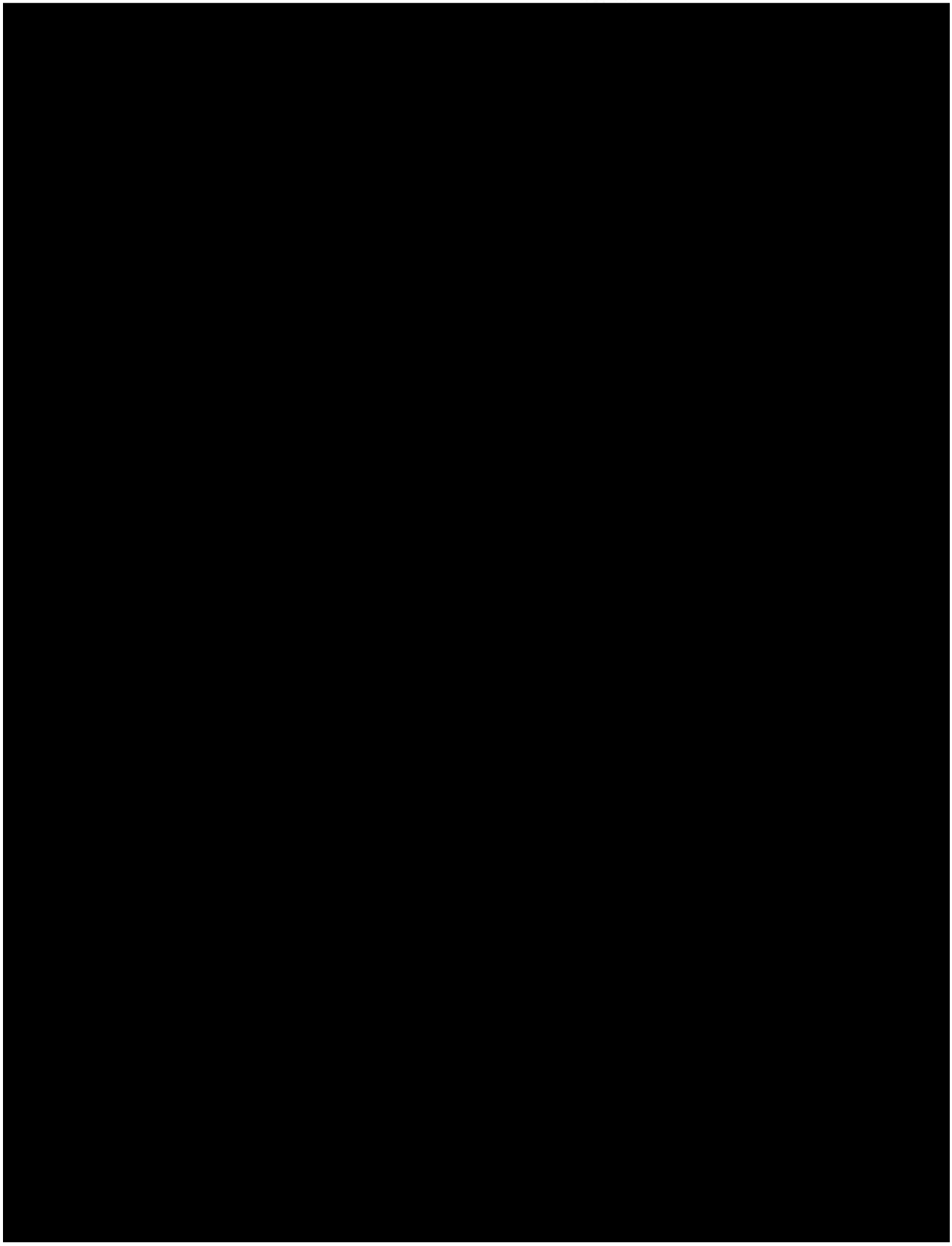
Part I: Nonmoto1· As pe ct s of Exp e rien c es of Dail y Li ving	**Part II: Motor Experiences of Daily Living**
Cognitive impainnent	Speech
Hallucinations and psychosis	Saliva and drooling
Depressed mood	Chewing and swallowing
Anxious mood	Eating tasks
Apathy	Dressing
Features of dopamine dysregulation syndrome	Hygiene
Sleep problems	Handwriting
Daytime sleepiness	Doing hobbies and other activities
Pain and other sensations	Tuming in bed
Urina1y problems	Tremor impact on activities
Constipation problems	Getting in and out of bed
Lightheadedness on standing	Walking and balance
Fatigue	Freezing
Part III: Motor Examination	**Part IV : Motor Complications**
Speech	Time spent with dyskinesias
Facial expression	Functional impact of dyskinesias
Rigidity (neck; right/left upper/lower extremities)	Painful *off* state dystonia
Finger tapping (right/left hands)	Time spent in the *off* state
Hand movements (right/left hands)	Functional impact of fluctuations
Pronation-supination movements of right/left hands	Complexity of motor functions
Toe tapping (right/left foot)	
Leg agility (right/left leg)	
Arising from chair	
Gait	
Freezing of gait	
Postural instability	
Posture	
Global spontaneity of movement (body bradykinesia)	
Postural tremor of right/left hands	
Kinetic tremor of right/left hands	
Rest tremor amplitude: right/left upper/lower extremities; lip jaw	
Constancyof rest tremor	

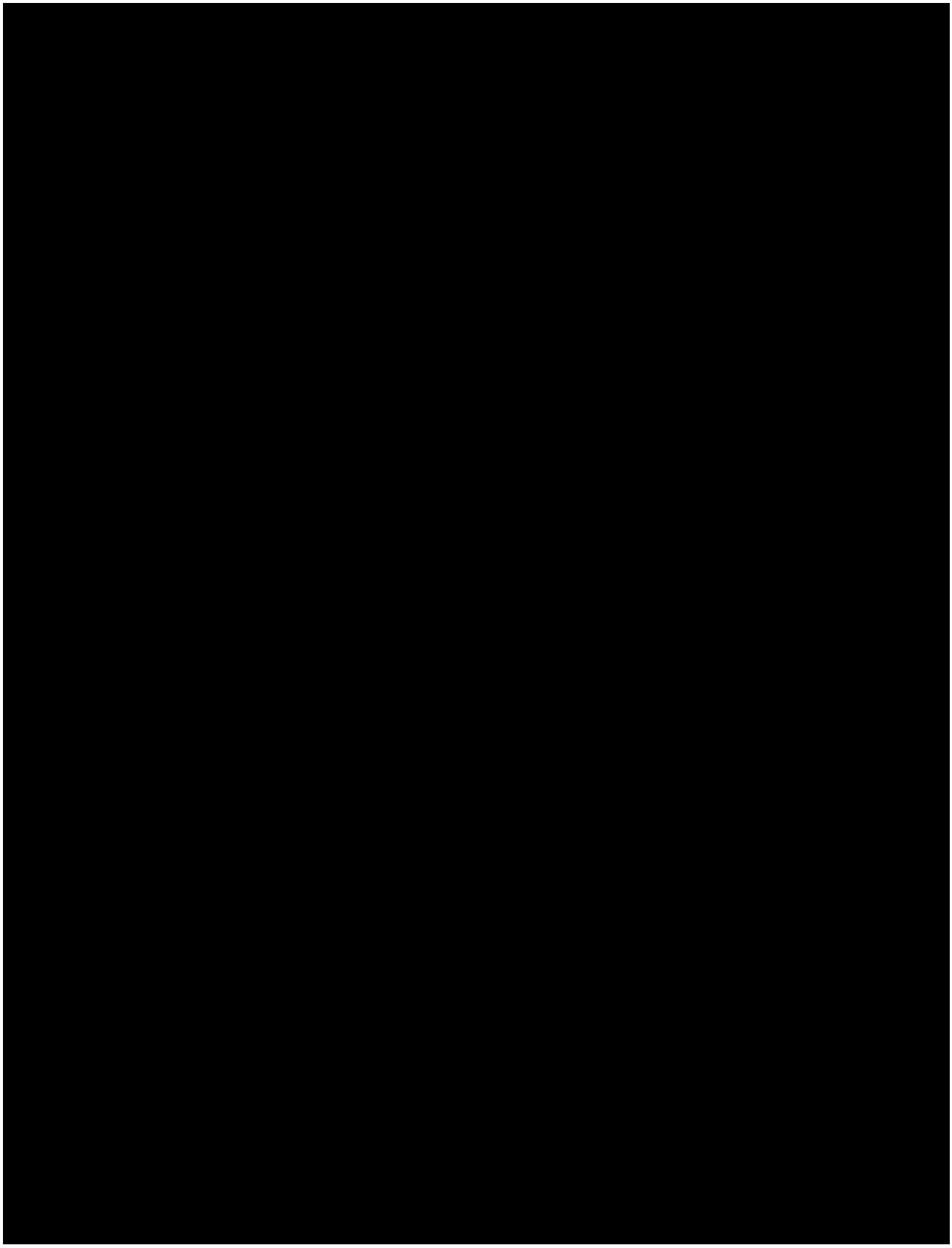
[redacted]

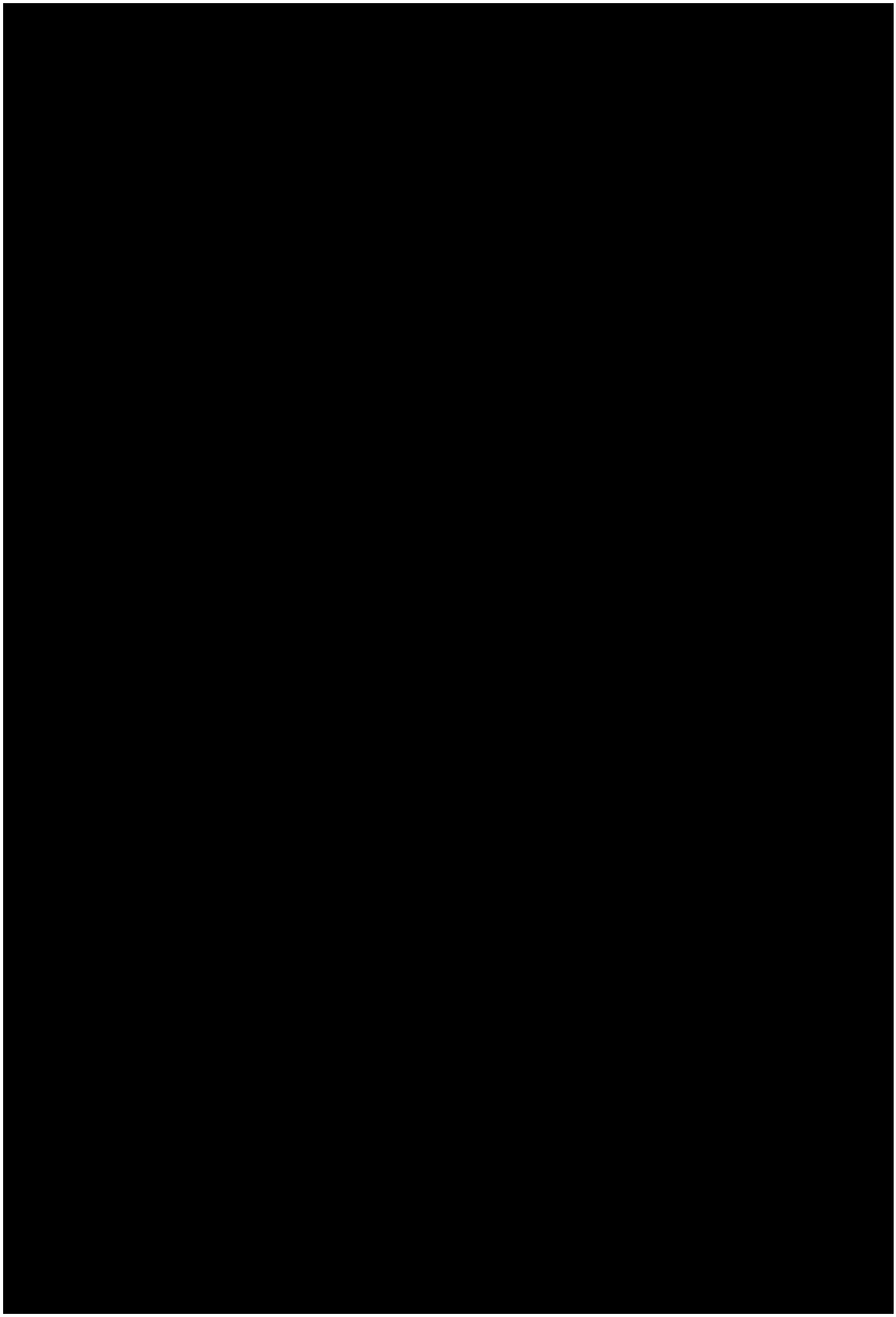


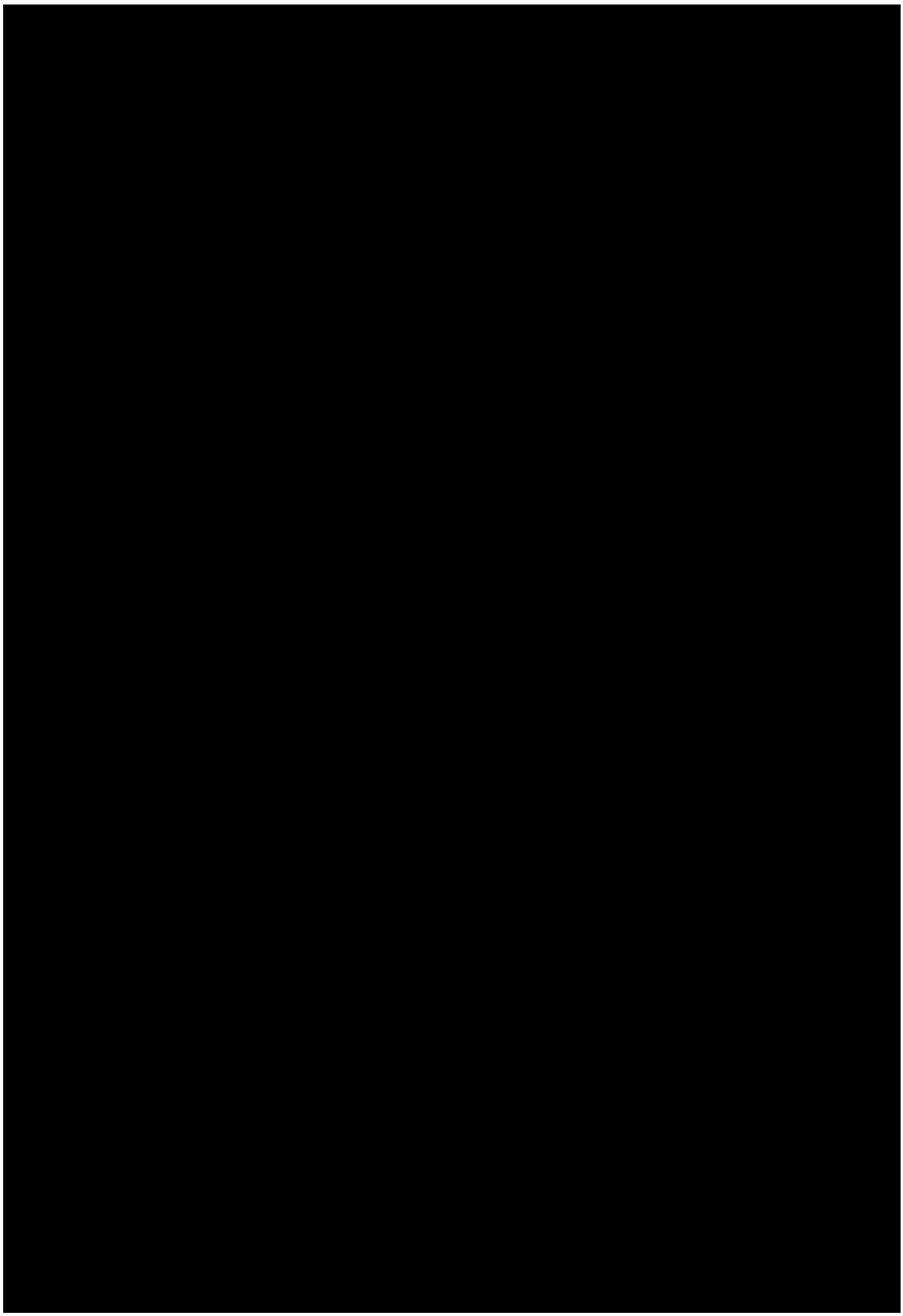












APPENDIX 9. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION AND SINCE LAST VISIT VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - *Most Severe Ideation:* _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - *Most Severe Ideation:* _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	

C-SSRS—Baseline/Screening (Version 1/14/09)
Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past__ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes No ☐ ☐ Total # of Attempts ____	Yes No ☐ ☐ Total # of Attempts ____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes No ☐ ☐	Yes No ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of interrupted ____	Yes No ☐ ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of aborted ____	Yes No ☐ ☐ Total # of aborted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes No ☐ ☐	Yes No ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes No ☐ ☐	Yes No ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Completed Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX 10. STANFORD SLEEPINESS SCALE (SSS)

This is a quick way to assess how alert you are feeling. If it is during the day when you go about your business, ideally you would want a rating of a one. Take into account that most people have two peak times of alertness daily, at about 9 a.m. and 9 p.m. Alertness wanes to its lowest point at around 3 p.m.; after that it begins to build again. Rate your alertness at different times during the day. If you go below a three when you should be feeling alert, this is an indication that you have a serious sleep debt and you need more sleep.

An Introspective Measure of Sleepiness
The Stanford Sleepiness Scale (SSS)

Degree of Sleepiness	**Scale Rating**
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

APPENDIX 11. MODIFIED OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (MOAA/S)

Modified Observer's Assessment of Alertness/Sedation Scale

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Summa ry of Changes Page
Protocol 217-PRK-201
Date 24 Oct 2016

The following changes, and the rationale for the changes, were made to the attached protocol in this amendment.

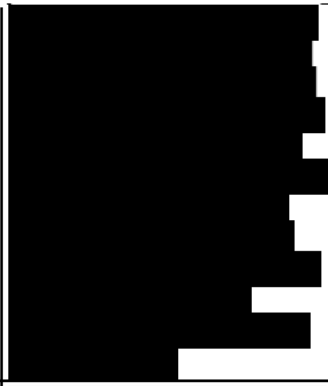
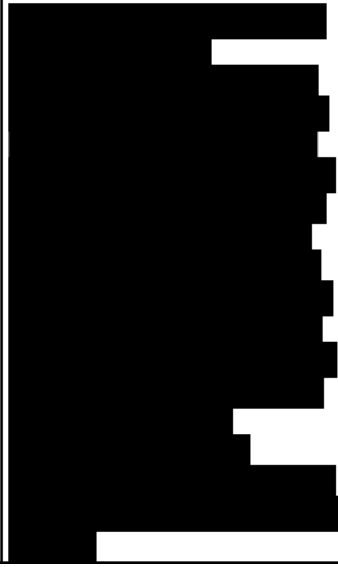
Section number and title in Amendment 1 (05 Oct 2016)	**Section number and title in Amendment 2 (24 Oct 2016)**	**Original text:**	**Changed to:**	**Rationale:**
Title Page	Title Page	Date of Original Protocol: 28 September 2016 Date of Amendment **1:** 05 October 2016	Date of Original Protocol: 28 September 2016 Date of Amendment 1: 5 October2016 **Date of Amendment 2:** **20 Octobe1· 2 01 6**	Added the date of Amendment 2 to the Title Page.
headers	headers	Version 2.0 05 October 2016	**Version 3.0 20 October**	Changed Version number and date to match those of Amendment 2 (version 3.0 20 October 2016)
Protocol Signature Page	Protocol Signature Page	Date of Amendment **1:** 5 October2016	**Date of Amendment 2:** **20 Octobe1· 2 01 6**	Revised the date of the signature page to be the date of Amendment 2.
Protocol Signature Page	Protocol Signature Page	[redacted], M.S. Sage Therapeutics	[redacted], PhD Sage Therapeutics	Changed the statistical signee.
Synopsis, Exploratory Endpoints And Section 6.3.3, Exploratory Endpoints	Synopsis, Exploratory Endpoints And Section 6.3.3, Exploratory Endpoints	[redacted]	[redacted]	[redacted]

Section number and title in Amendment 1 (05 Oct 2016)	**Section number and title in Amendment 2 (24 Oct 2016)**	**Original text:**	**Changed to:**	**Rationale:**
Synopsis, Methodology And Section 7.1 Overall Study Design (Part A) And Section 9.1.1, Part A	Synopsis, Methodology And Section 7.1 Overall Study Design (Part A) And Section 9.1.1 (Part A)	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 the following 3 days (Days 1 to 3).	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** the following 3 days (Days 1 to 3).	Revised text to clarify that only the morning dose of Levodopa was to be taken on Days 1 to 3.
Synopsis, Methodology And Section 7.1, Overall Study Design (Part B) And Section 9.1.2, Part B	Synopsis, Methodology And Section 7.1, Overall Study Design (Part B) And Section 9.1.2, Part B	Subjects randomized to the Levodopa plus placebo arm will receive Levodopa and SAGE 217 matching placebo oral solution in the AM for the first 4 days (Days 1 to 4).	Subjects randomized to the Levodopa plus placebo arm will receive Levodopa and SAGE 217 placebo oral solution in the AM for the first 4 days (Days 1 to 4).	Removed “matching” from placebo oral solution.
Synopsis, Inclusion Criteria And Section 8.1, Inclusion Criteria	Synopsis, Inclusion Criteria And Section 8.1, Inclusion Criteria	11. Female subjects must agree to practice a highly effective method of birth control while on study, and for 30 days after receiving the last dose of study drug.	11. Female subjects must agree to practice a highly effective method of birth control while on study **through completion of the last follow-up visit. If a subject discontinues early after receiving a dose of SAGE-217, then the subject must continue this method of birth control for at least 7 days following** the last dose of study drug.	Revised Inclusion Criterion 11 to clarify timing of highly effective method of birth control for females during the study and if a subject prematurely discontinued the study.
Synopsis, Inclusion Criteria And Section 8.1, Inclusion Criteria	Synopsis, Inclusion Criteria And Section 8.1, Inclusion Criteria	12. Male subjects must agree to practice a highly effective method of birth control while on study, and for 13 weeks after receiving the last dose of study drug. Effective methods of birth control include sexual abstinence, vasectomy, or a condom with spermicide	12. Male subjects must agree to practice a highly effective method of birth control while on study, and for 13 weeks after receiving the last dose of study drug. Effective methods of birth control include sexual abstinence, vasectomy, or a condom with spermicide	Revised wording of Inclusion Criterion 12 to specify that males and their partners must practice highly effective methods of birth control.

Section number and title in Amendment 1 (05 Oct 2016)	Section number and title in Amendment 2 (24 Oct 2016)	Original text:	Changed to:	Rationale:
		(men) in combination with female partner's highly effective method.	(men) in combination with **their** partner's highly effective method.	
Synopsis, Table 2 MDS-UPDRS (complete) and MDS-UPDRS (Part III only)	Synopsis, Table 2 MDS-UPDRS (complete) and MDS-UPDRS (Part III only)	MDS-UPDRS (complete) on Days 1,2, 3, 4, 7, and 14. MDS-UPDRS (Part III only) on Days 5 and 6. [redacted]	**Removed performance of MDS-UPDRS (complete) on Days 1,2,** 3, **4, and** 7, **and added** it **on Day 8.** **Added MDS-UPDRS (Part III only) to Days 1,** 2, **3, 4 , and** 7, **and removed it from Day 8.**	The MDS-UPDRS complete is to be perfo1med weekly, while the Part III assessment can be perfonned multiple times dw-ing a day.
[redacted]	[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Synopsis, Table 2, C-SSRS footnote	Synopsis, Table 2, C-SSRS footnote		**Added: 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.**	Clarified the version of the C-SSRS that should be used at each assessment.
Synopsis, Table 2, MDS-UPDRS (complete) footnote	Synopsis, Table 2, MDS-UPDRS (complete) footnote	Screening, Admission (Day-1), predose Day 1, Day 2, Day 3, and Day 4; postdose on Day 7; and Day 14	Screening, Admission (Day -1) **(only** if **time between Screening and Admission is** 7 **days), on Day 8 prio1· to re s uming Levodopa ,** and Day 14	The MDS-UPDRS complete is to be perfo1med weekly ; clarified that the MDS-UPDRS complete was to be perfo1med on Admission if at least 7 days had transpired since the screening assessment. Clarified that the Day 8 assessment was to be

Section number and title in Amendment 1 (05 Oct 2016)	Section number and title in Amendment 2 (24 Oct 2016)	Original text:	Changed to:	Rationale:
				performed prior to dosing with Levodopa.
Synopsis, Table 2, MDS-UPDRS (Pait III only) footnote	Synopsis, Table 2, MDS-UPDRS (Part III only) footnote	MDS-UPDRS (Part III only): 2 (± IO minute s) , 4 (±I O minutes), 8 (±15 minutes), and 12 (±15 minutes) hours postdose on Days 5, 6, and 8.	MDS-UPDRS (Pait III only): 2 (±10 minutes), 4 (± IO minu tes), 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 afte1· S creening , then the MDS-UPDRS Part** III **only should also take place on Admission (Day -1).**	The MDS-UPDRS complete is to be perfoimed weekly, while the Part III assessment can be perfonned multiple times dw·ing a day; revised timing of the complete and Pait III only assessments to align more closely with appropriate timing for these assessments. Clarified that the MDS-UPDRS Part III only was to be perfonned on Admission if less than 7 days had transpired since the scre.ening assess ment.
Synopsis, Table 3 MDS-UPDRS (complete) and MDS-UPDRS (Part III only)	Synopsis, Table 3 MDS-UPDRS (complete) and MDS-UPDRS (Part III only)	MDS-UPDRS (complete) on Days I, 4, 8, 15, and 22. MDS-UPDRS (Part III only) on Days 2, 3, 5, 6, 7, and 9.	**Removed performance of MDS-UPDRS (complete) on Days 1, 4, and 8, and added it on Day 9.** **Added MDS-UPDRS (Pa1·t** III **onl y) to Da ys 1, 4 , and 8, and removed it from Day 9.**	The MDS-UPDRS completeis to be perfoimed weekly, while the Part III assessment can be perfonned multiple times dw·ing a day; revised timing of the complete and Pait III only assessments to align more closely with appropriate timing for these assessments..
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S o sis, Table 3, MDS-	S o sis, Table 3, MDS-	Screenin , Admission	Screening, Admission	The MDS-UPDRS co lete is

Section number and title in Amendment 1 (05 Oct 2016)	Section number and title in Amendment 2 (24 Oct 2016)	Original text:	Changed to:	Rationale:
UPDRS (complete) footnote	UPDRS (complete) footnote	(Day-I), predose Day I and Day 4; postdose on Day 8; and Days 15 and 22	(Day - I) (**only** if time **between Screening and Admission is 7 days), on Day 9 pri01· to resuming Levodopa,** and Days 15 and 22.	to be perfo1med weekly ; clarifi ed that the MDS-UPDRS complete was to be perfo1med on Admission if at least 7 days had transpired since the screening assessment. Clarified that the Day 9 assessment was to be perfo1med prior to dosing with Levodopa.
Synopsis, Table 3, MDS-UPDRS (Pait III only) footnote	Synopsis, Table 3, MDS-UPDRS (Part III only) footnote	MDS-UPDRS (Part III only): 2 (± IO tninute s) , 4 (±IO minutes), 8 (±15 tninutes), and 12 (±15 minutes) hours postdose on Days 5, 6, and 8.	MDS-UPDRS (Patt III only): 2 (±10 tninutes), **3 (±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 Part** III **only should also take place on Admission (Day 1).** [redacted]	Added MDS-UPDRS (Part III only) assessments to align more closely with appropriate titning for this assessment; clarified that the MDS-UPDRS (Pait III only) was to be perfonned on Admission if less than 7 days had transpired since the scre ening ass essment. [redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Section number and title in Amendment 1 (05 Oct 2016)	Section number and title in Amendment 2 (24 Oct 2016)	Original text:	Changed to:	Rationale:
				
				

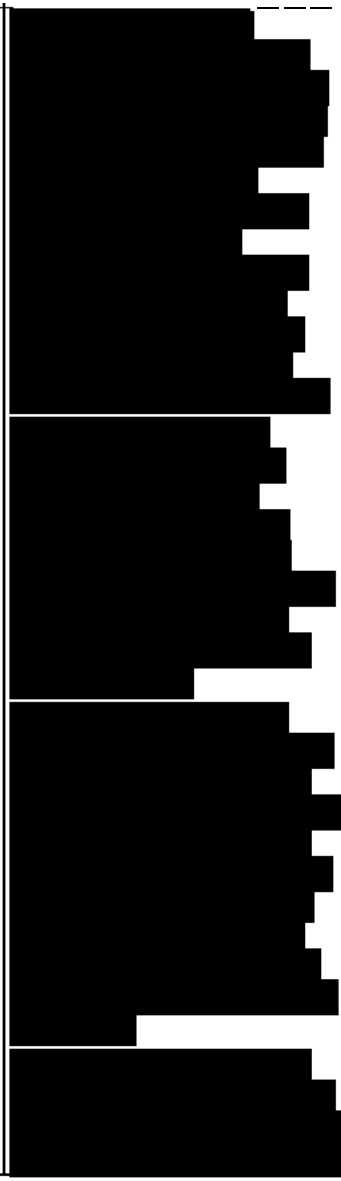
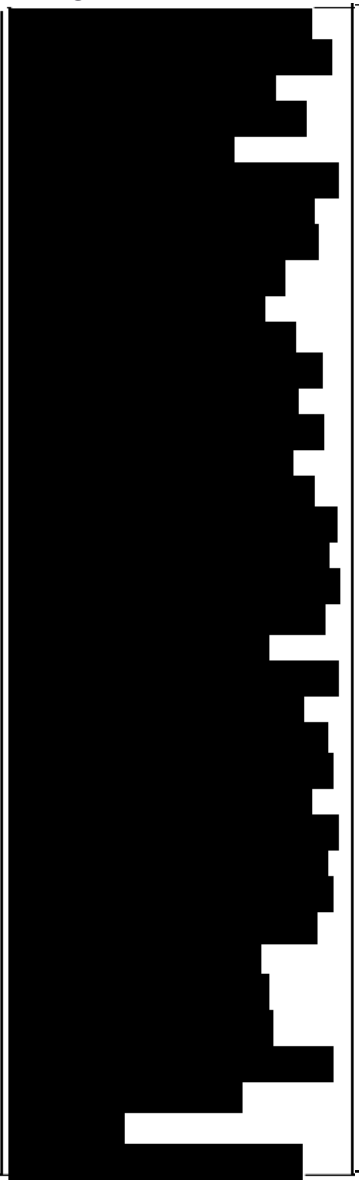
Section number and title in Amendment 1 (05 Oct 2016)	Section number and title in Amendment 2 (24 Oct 2016)	Original text:	Changed to:	Rationale:
Section 9.1.2, Part B	Section 9.1.2, Part B	Subjects randomized to the Levodopa plus SAGE-217 Oral Solution arm will receive this combination in the AM for the first 4 days (Days 1 to 4).	Subjects randomized to the Levodopa plus SAGE-217 Oral Solution arm will receive this combination in the AM for the first 4 days (Days 1 to 4). **Subjects will receive their individually established tolerated dose of SAGE-217 Oral Solution from Part A.**	Added the statement for consistency with next bullet: Subjects will receive their individually established tolerated dose of SAGE-217 Oral Solution from Part A.
Section 9.4, Randomization and Blinding	Section 9.4, Randomization and Blinding	Subjects will be randomly assigned in a 1:1 manner to one of two treatment groups: open-label Levodopa plus blinded SAGE 217 Oral Solution or matching placebo oral solution.	Subjects will be randomly assigned in a 1:1 manner to one of two treatment groups: open-label Levodopa plus blinded SAGE 217 Oral Solution or placebo oral solution.	Deleted "matching" from placebo oral solution.
Section 10.5, Administration	Section 10.5, Administration	SAGE-217 Oral Solution or matching placebo will be administered in the morning with food.	SAGE-217 Oral Solution or **placebo oral solution** will be administered in the morning with food.	Deleted "matching" from placebo and added oral solution.
Section 11.1, MDS-UPDRS	Section 11.1, MDS-UPDRS	The complete MDS-UPDRS is to be administered in Part A at screening, Admission (Day -1), predose on Days 1, 2, 3, and 4; postdose on Day 7; and on Day 14. The complete MDS-UPDRS is to be administered in Part B at screening, Admission (Day -1), predose on Days 1 and 4; postdose on Day 8; and on Days 15 and 22.	The complete MDS-UPDRS is to be administered in Part A at screening, Admission (Day -1), **on Day 8 prior to resuming Levodopa**, and on Day 14. The complete MDS-UPDRS is to be administered in Part B at screening, Admission (Day -1), **on Day 9 prior to resuming Levodopa**; and on Days 15 and 22. **In both Parts A and B, the Admission (Day -1) complete MDS-UPDRS is performed only if the time between Screening and Admission is**	Clarified that the Day 8 assessment in Part A and the Day 9 assessment in Part B were to be performed prior to dosing with Levodopa. The MDS-UPDRS complete is to be performed weekly while the Part III assessment can be performed multiple times during a day; clarified that the MDS-UPDRS complete was to be performed on Admission if at least 7 days had transpired since the screening assessment and the MDS-UPDRS (Part III only) was to

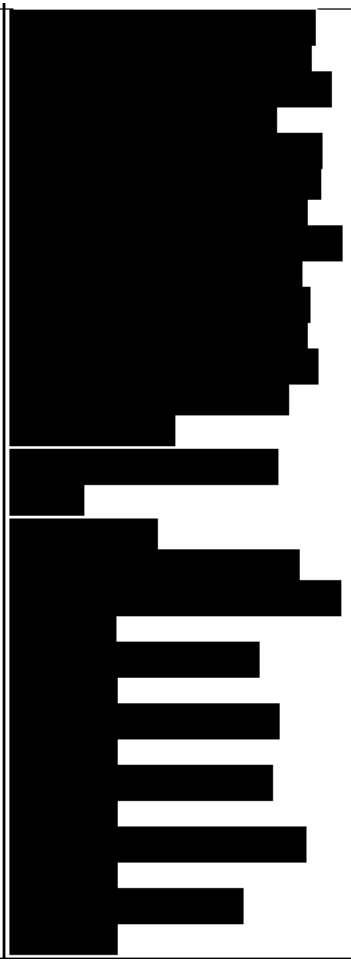
Section number and title in Amendment 1 (05 Oct 2016)	**Section number and title in Amendment 2 (24 Oct 2016)**	**Original text:**	**Changed to:**	**Rationale:**
			7 **days; otherwise, the MDS UPDRS Part** III **only is performed.**	be performed on Admission if less than 7 days had transpired since the screening assessment.
			Prut III of the MDS-UPDRS (motor examination) is to be completed in Part A at 2, 4, 8, and 12 hours postdose on Days **1, 2, 3, 4,** 5, 6, and 7, and in Pait B at 2, 3, 4,8, and 12 hours postdose on Days **1,** 2, 3, **4,** 5, 6, 7, and 9. If the **complete MDS-UPDRS is not performed on Admission due to Admission taking place** <7 **days after Screening, then Part** III **only should also take place on Admission (Day -1) for both Parts A and B.**	Added MDS-UPDRS (Part III only) assessments to align more closely with appropriate timing for this assessment; clrui·fied that the MDS-UPDRS complete was to be perfonned on Admission if at least 7 days had transpired since the scre ening ass ess men t and the MDS-UPDRS (Part III only) was to be perfonned on Admission if less than 7 days had transpired since the screening assessment.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Section number and title in Amendment 1 (05 Oct 2016)	Section number and title in Amendment 2 (24 Oct 2016)	Original text:	Changed to:	Rationale:

Sectionnumber and title in Amendment 1 (05 Oct 2016)	Section number and title in Amendment 2 (24 Oct 2016)	Original text:	Changed to:	Rationale:
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Section 14.4.2, Exploratory Efficacy Endpoints	Section 14.4.2, Exploratory Efficacy Endpoints	[redacted]	[redacted]	[redacted]

Section number and title in Amendment 1 (05 Oct 2016)	Section number and title in Amendment 2 (24 Oct 2016)	Original text:	Changed to:	Rationale:
		[redacted]	[redacted]	
Section 20, List of References	Section 20, List of References	Goetz CG, Poewe W, Rasco! 0 , et al. Movement Disorder Society Task Force Repo1t on the Hoehn and Yahr Staging Scale: Status and Recommendations. Mov Dis. 2004;19(9):I 020-8.	Deleted this reference.	The text related to this reference was deleted, so the reference was removed.
Appendix 2, Hoehn and Yahr Staging Criteria	Appendix 2, Hoehn and Yahr Staging Criteria	The original scale included 5 disease stages, numbered I to 5. The scale was later modified to include two intermediate stages (Goetz 2004). Table showing the modified Hoehn and Yahr Scale (includes additional stages of 0, 1.5, and 2.5)	The original scale included 5 disease stages, numbered **1** to 5.	The original scale was to be used. Deleted sentence about modified scale, deleted reference that was cited, and deleted table displaying modified scale.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Section number and title in Amendment 1 (05 Oct 2016)	Section number and title in Amendment 2 (24 Oct 2016)	Original text:	Changed to:	Rationale:
				

Section number and title in Amendment 1 (05 Oct 2016)	Section number and title in Amendment 2 (24 Oct 2016)	Original text:	Changed to:	Rationale:
				

1. TITLE PAGE

PROTOCOL NUMBER: 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

IND NUMBER: 131,258

Investigational Product	SAGE-217
Clinical Phase	2
Sponsor	Sage Therapeutics, Inc.
Sponsor Contact	[redacted], M.D., Ph.D. [redacted] Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: [redacted] Email: [redacted]
Medical Monitor	_ , M.D., M.P.H. Study Physician Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: [redacted] Email: [redacted]
Date of Odginal Protocol	28 September 2016
Date of Amendment 1	5 October2016

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

PROTOCOL SIGNATURE PAGE

Protocol Number:	217-PRK-201
Product:	SAGE-217 Oral Solution
IND No.:	131,258
Study Phase:	2
Sponsor:	Sage Therapeutics
Date of Amendment 1:	Version 2.0 05 October 2016

Sponsor Approval

[redacted]

[redacted] M.D., Ph.D.
Sage Th[redacted]

05 Oct 2016
Date (DD/MMMN YYY)

[redacted]
[redacted]arm.D., M.S., R.Ph.
[redacted]
Sage Therapeutics

5 Oct 2016
Date (DD/MMM/YYYY)

[redacted]
[redacted], MPH
[redacted]

05 Oct 2016
Date (DD/MMM/YYYY)

[redacted]
[redacted], M.S.
Statistician
Sage Therapeutics

05 OCT 2016
Date (DD/MMM/YYYY)

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the Clinical Protocol 217-PRK-201 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

CONTACTS IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Research Organization	[redacted]	[redacted]

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics
215 First Street
Cambridge, MA 02142

Name of Investigational Product:
SAGE-217 Oral Solution

Name of Active Ingredient:
SAGE-217

Title of Study: 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 (PD) of Moderate Severity Responding to Immediate-Release Levodopa/Carbidopa and Withdrawn from Levodopa/Carbidopa

Study centers: Up to 4 centers

Objectives:

Primary:

- To evaluate the safety and tolerability of SAGE-217 Oral Solution.

Secondary:

- 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.
- To compare the effect of SAGE-217 Oral Solution in combination with immediate-release oral Levodopa/Carbidopa to Levodopa/Carbidopa alone.

Endpoints:

Primary:

- Frequency and severity of adverse events and changes 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.

Secondary:

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) score.

Part B:

- Improvement in PD motor symptoms as assessed by changes in the MDS-UPDRS - Pait III score.
- Improvement in PD overall symptoms as assessed by changes in the MDS-UPDRS- Patts I-IV total score.
- Sleepiness/sedation as assessed by the Stanford Sleepiness Scale (SSS) and Modified Obse1ver's Assessment of Analgesia/Sedation (MOAAIS) scores.

In addition, plasma concentrations of SAGE-217 and possibly SAGE-217 metabolites will be measured, and PK paiameters will be derived.

Exploratory Endpoints:

[redacted]

Methodology:

This study will assess the safety, tolerability, pha1macokinetics (PK), and efficacy of SAGE-217 Oral Solution. For ease of discussion, Levodopa alone or Cai·bidopa-Levodopa combination will be refened to as Levodopa in this protocol.

There are two paits:

Part A: Open-label with morning (AM) dosing (4 days).

All subjects will continue to take their antipai·lcin so nian agents including immediate-release oral Levodopa on the day of admission (Day -1) and in the AM the following 3 days (Days 1 to 3). All subjects will stop their immediate-release oral Levodopa on Day 4 and will strut on a 30 mg dose of SAGE-217 Oral Solution administered in the AM with food. Subjects not tolerating 30 mg will receive 20 mg, and subjects not tolerating 20 mg will receive IO mg on subsequent days. The dose received on Day 7 will be defined as the tolerated dose for that subject. Subjects not tolerating IO 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 antipaikinsonian agent at Investigator's discretion) will be allowed, if needed, on all days (Days I to 7).

Pait A is designed to dete1mine the tolerated dose of SAGE-217 Oral Solution for each subject and to assess whether SAGE-217 exhibits efficacy in subjects with PD in order to info1m the conduct of Pait B.

Part B: Randoinized, lacebo-controlled, two-se uence crossover with AM dosin (u to 8 da s).

Part B will be initiated only after review of the Part A interim analysis.

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. Subjects randomized to the combination arm of Levodopa and SAGE-217 Oral Solution will receive this combination in the morning for the first 4 days (Days 1 to 4). Subjects randomized to the Levodopa plus placebo arm will receive Levodopa and SAGE-217 matching placebo oral solution 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).

All doses of SAGE-217 Oral Solution (or placebo) will be administered in the morning with food. If subjects are taking Levodopa as opposed to Carbidopa-Levodopa, administration with or without food will be determined by the Investigator.

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 adverse event 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 defined as 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 (Table 2 and Table 3, respectively).

Number of patients (planned):

Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14 to inform the conduct of Part B. Twelve subjects are anticipated to be randomized in Part B.

Diagnosis and main criteria for inclusion: All of the following inclusion and exclusion criteria will be applied during screening for Part A, with some of the criteria applied during screening for Part B, as indicated.

Inclusion criteria:

1. Subject has signed an informed consent form (ICF) before any study-specific procedures are performed.
2. Subject is between 40 and 75 years of age, inclusive.
3. Subject has a diagnosis of idiopathic PD based on modified UK Brain Bank Criteria (modified to allow individuals with a family history of PD) (Hughes 1992; Appendix 1).
4. Subjects with PD with a duration of less than 7 years and must meet the criteria for Hoehn and Yahr stage 2 or stage 3 (Appendix 2).
5. Subject has a stable dose of antiparkinsonian agents including immediate-release oral Levodopa or

Carbidopa-Levodopa (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.

6. Subject is willing to discontinue his/her treatment with immediate-release oral Levodopa or Carbidopa-Levodopa for at least 8 hours prior to dosing with SAGE-217. (Part B also)
7. Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) or amantadine at least 5 days prior to the day of admission (Day -1). (Part B also)
8. Subjects taking an antidepressant drug, sleep medication, or neuroleptic must have been on a stable dose for at least 1 month prior to the baseline visit.
9. Subjects must have a MoCA score of >22.
10. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests. (Part B also)
11. Female subjects must agree to practice a highly effective method of birth control while on study, and for 30 days after receiving the last dose of study drug. Highly effective methods of birth control include combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence. (Part B also)
12. Male subjects must agree to practice a highly effective method of birth control while on study, and for 13 weeks after receiving the last dose of study drug. Effective methods of birth control include sexual abstinence, vasectomy, or a condom with spermicide (men) in combination with female partner's highly effective method. (Part B also)
13. Males must be willing to abstain from sperm donation and females from donating eggs while on study through 13 weeks after receiving the last dose of study drug. (Part B also)

Exclusion criteria:

1. Subjects with a known hypersensitivity to SAGE-217 Oral Solution or its major excipient, HPβCD. (Part B also)
2. Subjects with early PD (Hoehn and Yahr stage 1) or advanced PD (Hoehn and Yahr stage 4 or stage 5).
3. Subjects with any medical or psychiatric condition that jeopardizes/compromises his/her ability for participation. This includes schizophrenia spectrum and other psychotic disorders, substance-related and addictive disorders, feeding and eating disorders, bipolar and related disorders, structural brain disease including but not limited to history of encephalitis or hydrocephalus and history of clinically significant stroke, or anticipating starting psychotherapy or behavior therapy during the course of the study or who started psychotherapy or behavior therapy within 30 days prior to Part A Day 1.
4. Subjects with a history of:
   a. Electroconvulsive therapy;
   b. Stereotaxic brain surgery (deep brain stimulation) for PD;
   c. History of suicide attempt within 2 years, or has answered YES to questions 3, 4, or 5 on the C SSRS at the screening or Day -1 visits, or has current suicidal ideation; or
   d. Impulse control disorder.
5. Subjects with severe depression as defined by a BDI-II score >19.
6. Subjects with Type I or Type II diabetes mellitus.
7. Subjects with presence of drug-induced parkinsonism (eg, metoclopramide, flunarizine), metabolic identified neurogenetic disorders (eg, Wilson's disease), encephalitis, or other atypical Parkinsonian syndromes (eg, progressive supranuclear palsy, multiple system atrophy). (Part B also)

8. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease. (Part B also)
9. Subject has clinically significant abnormal physical examination OR 12-lead ECG at the screening or admission visits. NOTE: QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study. ECG may be repeated once if initial values obtained are outside the specified limits. (Part B also)
10. Subject has a history, presence and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies 1 and 2.
11. Subject has exposure to another investigational medication or device within 30 days prior to Part A Day 1.
12. Subject has donated one or more units of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing (1 unit = 450 mL). (Part B also)
13. Subject is unwilling or unable to comply with study procedures. (Part B also)
14. Subjects has used any known strong inhibitors and/or inducers of cytochrome P450 (CYP)3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug. (Part B also)

Investigational product, dosage and mode of administration:

SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dose.

Duration of treatment: 7 days in Part A; 8 days in Part B

Part A:

Screening duration: up to 28 days; Treatment Period: 7 days; Follow-up: 7 days

Planned participation per subject: approximately 42 days during Part A.

Part B:

Screening duration: up to 14 days; Treatment Period: 8 days; Follow-up: 14 days

Planned participation per subject: approximately 36 days during Part B.

Reference therapy, dosage and mode of administration:

In part B, placebo will be matched to SAGE-217 Oral Solution.

Criteria for evaluation:

Safety and tolerability:

Safety and tolerability of study drug will be evaluated by vital signs, clinical laboratory measures, ECGs, physical examinations, concomitant medication usage, C-SSRS, and adverse event reporting. Sleepiness/sedation will be assessed by the SSS and MOAA/S.

Efficacy:

Improvement in PD motor symptoms and overall symptoms will be assessed by changes in the MDS-UPDRS Part III score and MDS-UPDRS Parts I-IV total score at various time points.

Pharmacokinetics:

Plasma will be collected to assay for concentrations of SAGE-217 and possibly SAGE-217 metabolites. The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), the distributional half-life and terminal half-life ($t_{1/2}$), and steady-state drug concentration in the plasma (C_{ss}).

Statistical methods:

Study Populations

The safety population, defined as all subjects who are administered study drug, will be used to provide descriptive summaries of safety.

The efficacy population, defined as all subjects in the safety population who receive at least one dose of study drug and have at least one postdose MDS-UPDRS evaluation, will be used to analyze efficacy data.

The PK population will consist of all subjects in the safety population with sufficient plasma concentrations for PK evaluations and will be used to summarize PK data.

Separate populations will be defined for each part of the study.

General Considerations

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

Safety Analysis

Adverse events will be coded using Medical Dictionary for Regulatory Activities™ (MedDRA). The overall incidence of adverse events will be displayed by System Organ Class (SOC), preferred term, dose group, and cohort. Incidence of adverse events will also be presented by maximum severity and relationship to study drug. Vital signs, clinical laboratory measures, ECG, and C-SSRS data will be summarized by dose group and cohort, where applicable. Out-of-range safety endpoints may be categorized as low or high, where applicable.

Efficacy Analysis

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data.

An interim analysis of 10 subjects completing Part A is planned to inform Part B study conduct.

Pharmacokinetic Analysis

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics and listed by subject.

Table 2: Schedule of Events: Part A (Open-Label)

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	X	X			X		X
MDS-UPDRS (Part III only)[k]							X	X		X	

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)
[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 Admission (Day -1); predose for Day 4, Day 6, and Day 8; and Day 14

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

[d] Vital Signs: Screening and 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. 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.

[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 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), predose Day 1, Day 2, Day 3, and Day 4; postdose on Day 7; 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 5, 6, and 8.

[p] Plasma PK sampling times (±5 minutes): Day 4 predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose; predose 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

Table 3: Schedule of Events: Part B (Randomized, Placebo-Controlled)

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		X	X
MDS-UPDRS (Part III only)[k]				X	X		X	X	X		X		
[redacted]													

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
[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] 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), predose on Day 1 and Day 4; postdose on Day 8; and Days 15 and 22.

[k] MDS-UPDRS (Part III only): 2 (±10 minutes), 4 (±10 minutes), 8 (±15 minutes), and 12 (±15 minutes) hours postdose on Days 2, 3, 5, 6, 7, and 9.

[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.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

1. TITLE PAGE 1
2. SYNOPSIS 6
3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 18
4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 25
5. INTRODUCTION 27
5.1. Background of Parkinson's Disease and Unmet Medical Need 27
5.2. SAGE-217 Oral Solution 28
5.3. Summary of Nonclinical and Clinical Experience with SAGE-217 28
5.3.1. Nonclinical Studies with SAGE-217 28
5.3.2. Clinical Experience 28
5.4. Potential Risks and Benefits 30
6. TRIAL OBJECTIVES AND PURPOSE 31
6.1. Primary Objective 31
6.2. Secondary Objectives 31
6.3. Endpoints 31
6.3.1. Primary Endpoints 31
6.3.2. Secondary Endpoints 31
6.3.3. Exploratory Endpoints 31
7. INVESTIGATIONAL PLAN 33
7.1. Overall Study Design 33
7.2. Number of Subjects 34
7.3. Treatment Assignment 34
7.4. Dose Adjustment Criteria 35
7.5. Criteria for Study Termination 35
8. SELECTION AND WITHDRAWAL OF SUBJECTS 37
8.1. Subject Inclusion Criteria 37
8.2. Subject Exclusion Criteria 38
8.3. Entrance Criteria for Part B 39
8.4. Subject Withdrawal Criteria 39

9. TREATMENT OF SUBJECTS 40
9.1. Description of Study Drug 40
9.1.1. Part A 40
9.1.2. Part B 40
9.2. Concomitant Medications 40
9.2.1. Prior/Concomitant Medications 40
9.2.2. Prohibited Medications 41
9.3. Treatment Compliance 41
9.4. Randomization and Blinding 41
10. STUDY DRUG MATERIALS AND MANAGEMENT 43
10.1. Study Drug 43
10.2. Study Drug Packaging and Labeling 43
10.3. Study Drug Storage 43
10.4. Study Drug Preparation 44
10.5. Administration 44
10.6. Study Drug Accountability 45
10.7. Study Drug Handling and Disposal 45
11. ASSESSMENT OF EFFICACY 46
11.1. Movement Disorder Society – Unified Parkinson's Disease Rating Scale 46
11.2. Exploratory Endpoints 47
[redacted] [redacted] 47
[redacted] [redacted] 47
[redacted] [redacted] 47
[redacted] [redacted] 48
[redacted] [redacted] 48
12. PHARMACOKINETICS 50
12.1. Blood Sample Collection 50
12.2. Storage and Shipment of Pharmacokinetic Samples 50
12.3. Sample Analysis 50
13. ASSESSMENT OF SAFETY 51
13.1. Safety and Tolerability Parameters 51
13.1.1. Demographic/Medical History 51
13.1.2. Vital Signs 51

13.1.3. Weight and Height 51
13.1.4. Physical Examination 51
13.1.5. Electrocardiogram (ECG) 51
13.1.6. Laboratory Assessments 52
13.1.6.1. Hematology 52
13.1.6.2. Blood Chemistry 52
13.1.6.3. Urinalysis 52
13.1.6.4. Virus Serology 52
13.1.6.5. Pregnancy Screen 53
13.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS) 53
13.1.8. Stanford Sleepiness Scale (SSS) 53
13.1.9. Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) 53
13.2. Adverse and Serious Adverse Events 54
13.2.1. Definition of Adverse Events 54
13.2.1.1. Adverse Event 54
13.2.1.2. Suspected Adverse Reaction 54
13.2.1.3. Serious Adverse Event 54
13.2.1.4. Recording Sedation as an Adverse Event 55
13.2.2. Pregnancy 55
13.3. Relationship to Study Drug 55
13.4. Recording Adverse Events 56
13.5. Reporting Serious Adverse Events 56
14. STATISTICAL METHODS AND CONSIDERATIONS 58
14.1. Data Analysis Sets 58
14.2. Handling of Missing Data 58
14.3. Demographics and Baseline Characteristics 58
14.4. Efficacy Endpoints 58
14.4.1. Secondary Efficacy Endpoints 58
14.4.2. Exploratory Efficacy Endpoints 58
14.5. Safety and Tolerability Analyses 59
14.5.1. Adverse Events 59
14.5.2. Vital Signs 59
14.5.3. Physical Examinations 59

14.5.4. 12-Lead ECG 60
14.5.5. Clinical Laboratory Evaluations 60
14.5.6. Columbia-Suicide Severity Rating Scale (C-SSRS) 60
14.5.7. Stanford Sleepiness Scale (SSS) 60
14.5.8. Modified Observer's Assessment of Alertness/Sedation (MOAA/S) 60
14.5.9. Prior and Concomitant Medications 60
14.6. Pharmacokinetic Analysis 61
14.7. Determination of Sample Size 61
14.8. Changes From Protocol Specified Analyses 61
15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS 62
15.1. Study Monitoring 62
15.2. Audits and Inspections 62
15.3. Institutional Review Board (IRB) 63
16. QUALITY CONTROL AND QUALITY ASSURANCE 64
17. ETHICS 65
17.1. Ethics Review 65
17.2. Ethical Conduct of the Study 65
17.3. Written Informed Consent 65
18. DATA HANDLING AND RECORDKEEPING 66
18.1. Inspection of Records 66
18.2. Retention of Records 66
18.3. Confidentiality 66
19. PUBLICATION POLICY 68
20. LIST OF REFERENCES 69
21. APPENDICES 71
APPENDIX 1. UNITED KINGDOM BRAIN BANK CRITERIA 72
APPENDIX 2. HOEHN AND YAHR STAGING CRITERIA 73
APPENDIX 3. ANTICHOLINERGIC DRUGS 74
APPENDIX 4. MOVEMENT DISORDER SOCIETY-UNIFIED PARKINSON'S DISEASE RATING SCALE (MDS-UPDRS) 75
[redacted] 76
[redacted] 77
[redacted] 80

[redacted] 81
APPENDIX 9. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION AND SINCE LAST VISIT VERSION 84
APPENDIX 10. STANFORD SLEEPINESS SCALE (SSS)..... 90
APPENDIX 11. MODIFIED OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (MOAA/S)..... 91

LIST OF TABLES

Table 1: Emergency Contact Information 5
Table 2: Schedule of Events: Part A (Open-Label) 12
Table 3: Schedule of Events: Part B (Randomized, Placebo-Controlled) 15
Table 4: Abbreviations and Specialist Terms 25
Table 5: Batch Formula for 125 mL of Stock SAGE-217 Oral Solution 6 mg/mL 44
Table 6: Rating Scale for the MDS-UPDRS 46

LIST OF FIGURES

Figure 1: Study Design of Part A 36
Figure 2: Study Design of Part B 36

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ALT	alanine aminotransferase
AM	morning
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
[redacted]	[redacted]
BMI	body mass index
CBC	complete blood count
C_{max}	maximum plasma concentration
CRF	case report form
CS	clinically significant
Css	steady-state drug concentration in the plasma
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic CRF
EP	European Pharmacopeia
GABA	γ aminobutyric acid
$GABA_A$	γ aminobutyric acid-ligand gated chloride channel
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPβCD	hydroxypropyl-β-cyclodextrin
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
Levodopa/Carbidopa	Levodopa or Carbidopa-Levodopa
MDS	Movement Disorder Society
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
MoCA	Montreal Cognitive Assessment
MTD	maximum tolerated dose
n	number
NCS	not clinically significant
NF	National Formulary
PD	Parkinson's disease
[redacted]	[redacted]
PK	pharmacokinetic(s)
PM	evening
QTcF	QT interval calculated using the Fridericia method
SOC	system organ class
SRC	Safety Review Committee
SSS	Stanford Sleepiness Scale
TEAE	treatment-emergent adverse event
$t_{1/2}$	terminal half-life
t_{max}	time to reach maximum concentration
USP	United States Pharmacopeia
WHO	World Health Organization

5. INTRODUCTION

5.1. Background of Parkinson's Disease and Unmet Medical Need

Parkinson's disease (PD) is a chronic progressive neurodegenerative condition that affects the motor, autonomic, cognitive, and sensory systems. Parkinson's disease is the second most common neurodegenerative disorder (Bergman 2002) and is associated with a massive loss of dopaminergic cells in the substantia nigra, leading to dopamine hypofunction and alteration of the basal ganglia circuitry. Dopamine neurons are under the control of the excitatory glutamatergic and inhibitory γ-aminobutyric acid (GABA) systems. Imbalance between the glutamatergic and GABA systems may contribute to excitotoxicity and dopaminergic cell death.

The motor symptoms of PD have been linked with a loss of dopamine neurons in the substantia nigra pars compacta and a consequential reduction in the level of dopamine input in the striatum (Siderowf 2012). These symptoms evolve slowly and are characterized by the progression of tremor, rigidity, bradykinesia, and postural instability. Tremor caused by PD can appear as either a resting tremor or an action tremor. The most typical tremor of PD is a "pill-rolling" rest tremor between the thumb and index finger. Not everyone with PD develops a tremor, and those who do experience tremor may have symptoms that come and go. Typically, PD tremor starts in the fingers of one hand before spreading to affect the rest of the arm. Tremor can also spread to affect the foot on the same side of the body and, after several years, the tremor can spread to affect the other side of the body. Without treatment, PD tremor usually worsens over time.

At present, there is no cure for PD. The core symptoms are caused by the degeneration of dopamine-producing neurons and, therefore, treatment consists of dopamine replacement. While enormous progress has been made in the treatment of PD over the past half century, levodopa remains the most potent drug for controlling PD symptoms (Jankovic 2008). The addition of carbidopa, a peripheral dopa decarboxylase inhibitor, enhances the therapeutic benefits of levodopa. However, levodopa therapy is frequently associated with motor complications, and the appropriate time to initiate levodopa therapy continues to be debated (Stern 2004; Weiner 2004). The majority of patients treated with levodopa experience motor fluctuation, dyskinesia or other complications after 5 years of treatment (Jankovic 2005).

Neurosteroids, a group of steroid hormones synthesized in the brain, modulate the function of several neurotransmitter systems. The substantia nigra expresses high concentrations of allopregnanolone, a neurosteroid that positively modulates the action of GABA at γ-aminobutyric acid-ligand gated chloride channel ($GABA_A$) receptors. In PD patients, decreased plasma and cerebrospinal fluid levels of the neurosteroid allopregnanolone and 5α-dihydroprogesterone have been observed (di Michele 2003).

Parkinson's disease is the second most common chronic neurodegenerative disease, affecting about 1 million people in the United States and more than 4 million people worldwide. It has a devastating effect on patients and is often accompanied by tremendous physical and emotional burden not only for the patients but also for their families and friends. As the size of the elderly population grows, the burden of PD is projected to grow substantially over the next few decades. To date, the therapy of PD is symptomatic, aimed at ameliorating motor symptoms. Although the goal of therapy is to reverse the functional disability, abolition of all symptoms and signs is

not currently possible, even with high doses of medication. Thus, there is a growing need for innovative new treatments to prevent, delay onset, or alleviate symptoms of PD. Neurosteroids act as neuroprotectants and as $GABA_A$-receptor agonists in the physiology and pathology of the basal ganglia, impact dopaminergic cell activity and survival, and may therefore represent potential therapeutics in PD.

5.2. SAGE-217 Oral Solution

SAGE-217 is a positive allosteric modulator of the $GABA_A$ receptor and thus is expected to be of benefit for the treatment of PD.

SAGE-217 Oral Solution 6 mg/mL (40% w/w aqueous hydroxypropyl-β-cyclodextrin [HPβCD] with 0.025 mg/mL sucralose) is a non-viscous, clear solution.

5.3. Summary of Nonclinical and Clinical Experience with SAGE-217

5.3.1. Nonclinical Studies with SAGE-217

In nonclinical studies of SAGE-217, sedative-hypnotic effects were consistently observed at higher doses in both in vivo pharmacology studies and in toxicology studies. The sedative-hypnotic impairments seen with SAGE-217 were typical for $GABA_A$-positive modulators, ranging from hyperexcitability and ataxia at the lower doses through deep sedation and ultimately anesthesia at higher doses. Depth and duration of sedation demonstrated a clear dose response over the range tested, with evidence of tolerance occurring with continued exposure. Tolerance to the effects of SAGE-217 on motor incoordination was not observed after 7 days of dosing.

The compound has been assessed in 14-day rat and dog toxicology studies with daily administration of SAGE-217 as a solution in HPβCD in dogs and Labrasol® in rats. The no observed adverse effect level was 3 mg/kg (females) and 22.5 mg/kg (males) in rats and 2.5 mg/kg in dogs. There were no adverse effects in dogs or rats in the main toxicology studies. A single observation of mortality occurred in one female rat at the high dose in a toxicokinetic study that was suspected to have been related to exaggerated pharmacology. Additional toxicology and pharmacology information is provided in the Investigator's Brochure.

5.3.2. Clinical Experience

To date, two clinical studies employing SAGE-217 Oral Solution are clinically complete and final clinical study reports are pending. Discussions of pharmacokinetic (PK) data are limited to the single-ascending dose, food effect, and essential tremor cohorts from Study 217-CLP-101 and the multiple-ascending dose and drug-drug interaction cohorts from Study 217-CLP-102. Discussions of safety data are limited to the single-ascending dose cohorts in Study 217 CLP 101 and the multiple-ascending dose cohorts in Study 217-CLP-102.

Study 217-CLP-101 was a first-in-human, four-part study that assessed the effects of a single dose of SAGE-217. The study was a double-blind, placebo-controlled, single-ascending dose design in healthy adult volunteers, with the objective of identifying the maximum tolerated dose (MTD) and PK profiles of SAGE-217 Oral Solution. Subjects in each of the single-ascending dose cohorts received a single dose of study drug, either SAGE-217 (six subjects) or placebo (two subjects), with SAGE-217 doses of 0.25 mg, 0.75 mg, 2 mg, 5.5 mg, 11 mg, 22 mg, 44 mg,

55 mg, and 66 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the Safety Review Committee (SRC) and agreement reached that it was safe to increase the dose. The MTD was determined to be 55 mg. Two cohorts, 6 subjects each, received SAGE-217 Oral Solution in an open-label manner (one cohort received 50% of the MTD [22 mg] to study the food effects and the other cohort received the MTD [55 mg] to study the effects on subjects with essential tremor). SAGE-217 Oral Solution was orally bioavailable, demonstrated dose-linear PK from the lowest (0.25 mg) through the highest (66 mg) dose, and supported once-daily oral dosing with food. In addition, the pharmacodynamic effects of the SAGE-217 Oral Solution MTD were assessed in placebo-controlled, blinded, crossover electroencephalogram cohorts of 8 subjects each; one cohort received 50% of the MTD (22 mg) and the other received the MTD (55 mg).

Study 217-CLP-102 was a two-part study that assessed the effects of multiple-ascending doses of SAGE-217 Oral Solution. The study was a double-blind, placebo-controlled, multiple-ascending dose study in healthy adult volunteers. Subjects in each of the multiple-ascending dose cohorts received study drug, either SAGE-217 (nine subjects) or placebo (three subjects), once daily for 7 days, with SAGE-217 Oral Solution doses of 15 mg, 30 mg, and 35 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the SRC and agreement reached that it was safe to increase the dose. The MTD was determined to be 30 mg. It was observed that subjects receiving the drug in the evening did better in terms of tolerability compared to when they received the drug in the morning. A fourth cohort of 12 subjects received 30 mg of SAGE-217 Oral Solution in an open-label manner to study drug-drug interactions. SAGE-217 Oral Solution is not likely to induce the metabolism of cytochrome P450 (CYP)2B6 or CYP3A4 substrates. SAGE-217 Oral Solution was orally bioavailable and suitable for once-daily oral dosing at night time with food.

SAGE-217 Oral Solution was generally well tolerated. In both Phase 1 studies (217-CLP-101 and 217-CLP-102), doses were escalated until the stopping criteria were met. Most adverse events were reported as mild or moderate in intensity, and there were no serious adverse events reported in either study. In addition, none of the observed adverse events resulted in discontinuation of the study drug. At doses planned for further study, the observed sedation was mild, transient, and associated with daily peak exposure. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, dizziness, euphoric mood, fatigue, tremor, and muscle twitching, reported most frequently in the highest dose group (66 mg). Some changes in mean blood pressure and heart rate were observed after single doses of 44 mg and greater. After multiple doses of 30 mg (morning [AM] or evening [PM]) or 35 mg (AM) over 7 days, there was no evidence of changes in mean vital sign measures even though Day 7 plasma concentrations approximated that of the highest single dose in the single-ascending dose study. Subjects seemed to tolerate SAGE-217 better when given as night time dosing.

Neuroactive steroids are a class of endogenous and synthetic positive allosteric modulators that target both synaptic and extra-synaptic $GABA_A$ receptors (Belelli 2002 and confirmed in the Sponsor's in vitro studies). This diverse activity profile suggests that neuroactive steroid $GABA_A$ receptor-positive allosteric modulators could exhibit robust activity against essential tremor. Administration of SAGE-547 injection, a proprietary formulation of the endogenous neuroactive steroid, resulted in significant reductions in upper limb kinetic tremor scores compared to placebo in a Phase 2 proof-of-principle study (IND 122,280). Based on these

results with SAGE-547, the study design for single-ascending dose study 217-CLP-101 included a cohort of subjects with essential tremor (N=6) who received SAGE-217 Oral Solution (55 mg) in an open-label manner. Data from this cohort indicate that single doses of SAGE-217 Oral Solution resulted in a reduction in the tremor symptoms, suggesting that SAGE-217 might be effective in treating PD.

There are no clinical efficacy data of SAGE-217 Oral Solution in PD, since the present study is the first study in this indication.

5.4. Potential Risks and Benefits

Protocol 217-PRK-201 is the first clinical study evaluating the efficacy of SAGE-217 Oral Solution in PD. Thus, the potential benefits in this population are unknown, although the risks are likely to be similar to those mentioned in the Investigator's Brochure. GABA compounds that cross the blood-brain barrier or increase GABA activity alleviate muscle stiffness caused by a lack of GABAergic tone (Winkler 1999), validating this receptor as a therapeutic target. Given the promising clinical data with another neuroactive steroid (SAGE-547) in conjunction with the shared broad receptor selectivity profile, oral bioavailability, long half-life, preclinical evidence of anxiolytic activity, and safety data of SAGE-217, it is possible that patients may have a clinical benefit at the exposures selected for this study. In view of the few risks associated with administration of SAGE-217 Oral Solution that have been identified to date, an intra-patient dose-reduction design has been chosen to permit reduction in dose based on tolerability (adverse events), specifically sedation, versus treatment effect. Each subject will start with an initial dose of 30 mg; subjects unable to tolerate 30 mg will receive 20 mg; subjects unable to tolerate 20 mg will receive 10 mg. The tolerated dose for each subject will be the dose taken on Day 7. Subjects who tolerate at least the 10 mg dose on Day 7 will be eligible to enroll in Part B. Given the high medical need and potential for benefit in PD, there is a favorable benefit-risk evaluation to investigate SAGE-217 Oral Solution in PD.

In conclusion, selection criteria for the proposed study take into account the potential safety risks. Continuous safety monitoring, and the implementation of a formal dose-reduction and study drug discontinuation scheme also have the potential to mitigate risk. From a benefit/risk perspective, the appropriate measures are being taken in order to ensure the safety of the subjects who will be enrolled.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of SAGE-217 Oral Solution.

6.2. Secondary Objectives

The secondary objectives of the study 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.
- To compare the effect of SAGE-217 Oral Solution in combination with immediate-release oral Levodopa/Carbidopa to Levodopa/Carbidopa alone.

6.3. Endpoints

6.3.1. Primary Endpoints

- Frequency and severity of adverse events and changes in vital signs, clinical laboratory data, electrncardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS) during both Part A and Pait B.

6.3.2. Secondary Endpoints

Part A:

- Improvement in PD motor symptoms as assessed by changes in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) - Pali III (Motor Examination) score.

Part B:

- Improvement in PD motor symptoms as assessed by changes in the MDS-UPDRS - Pait III score.
- Improvement in PD overall symptoms as assessed by changes in the MDS-UPDRS - Palis I-IV total score.
- Sleepiness/sedation as assessed by the Stanford Sleepiness Scale (SSS) and Modified Observer's Assessment of Analgesia/Sedation (MOAA/S) scores.

6.3.3. Exploratory Endpoints

I [redacted]

I [redacted]

I [redacted]

I [redacted]

I [redacted]

7. INVESTIGATIONAL PLAN

For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol.

7.1. Overall Study Design

This study is a two-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 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 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 morning with food, as outlined in Section 9.1.1. 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). 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 interim analysis.

  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 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. Subjects randomized to the Levodopa plus placebo arm will receive Levodopa and SAGE-217 matching 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 adverse event 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 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 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.

The study designs of Part A and Part B are displayed in Figure 1 and Figure 2, respectively. Assessments will be performed periodically during the study as outlined in the Schedule of Events for Part A and Part B (Table 2 and Table 3, respectively).

7.2. Number of Subjects

Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14 to inform the conduct of Part B. Twelve subjects are anticipated to be randomized in Part B.

7.3. Treatment Assignment

SAGE-217 will be administered in the morning with food in Parts A and B. Food intake will be standardized as specified by the Sponsor. If subjects are taking Levodopa as opposed to Carbidopa-Levodopa, administration with or without food will be determined by the Investigator.

Part A of the study is open-label. Part B of the study is randomized, placebo-controlled, two-sequence crossover. Subjects will be randomly assigned in a 1:1 manner to receive open-label Levodopa plus blinded SAGE-217 Oral Solution or placebo for 4 days (Days 1 to 4, Period 1 of crossover). Subjects, clinicians, and the study team will be blinded to treatment allocation. The pharmacist, who will prepare the oral solutions according to the randomization schedule, will be

unblinded. For the remaining 4 days of Part B (Days 5 to 8, Period 2 of crossover), all subjects will discontinue Levodopa and will receive their individually established tolerated dose of SAGE-217 Oral Solution from Part A in an open-label manner.

Dose reductions for lack of tolerability will be allowed during both parts of the study (Section 7.4).

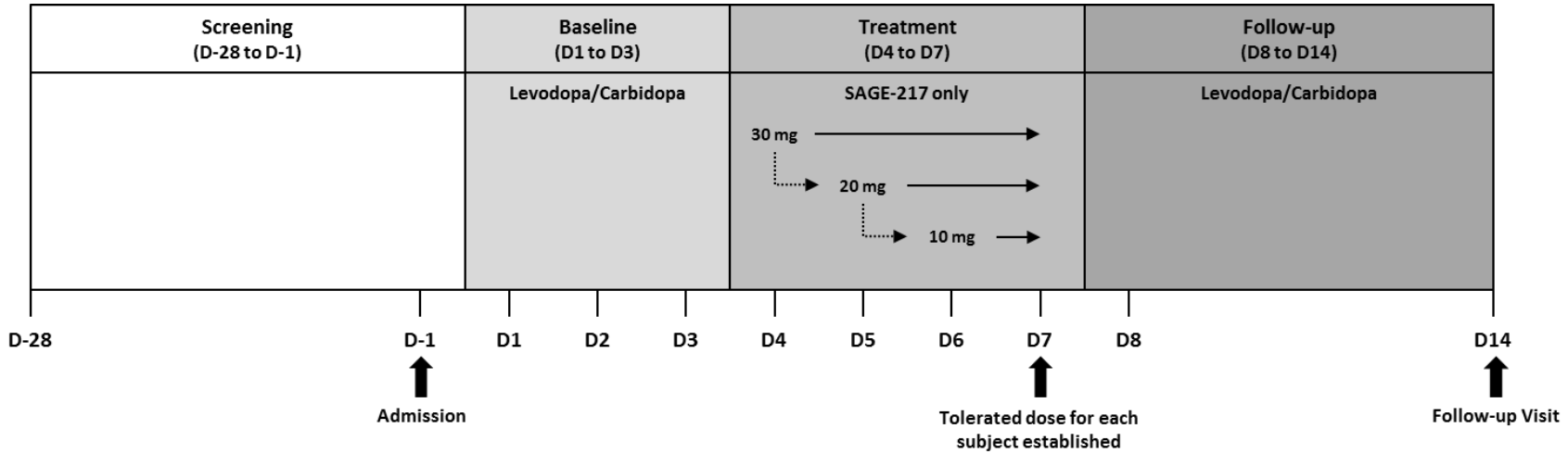
7.4. Dose Adjustment Criteria

Dose reductions of SAGE-217 for lack of tolerability will be allowed during both parts of the study. If at any time the dose is not tolerated in Part A, as determined by the Investigator, the dose on the next day will be reduced to the next lowest dose (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 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

7.5. Criteria for Study Termination

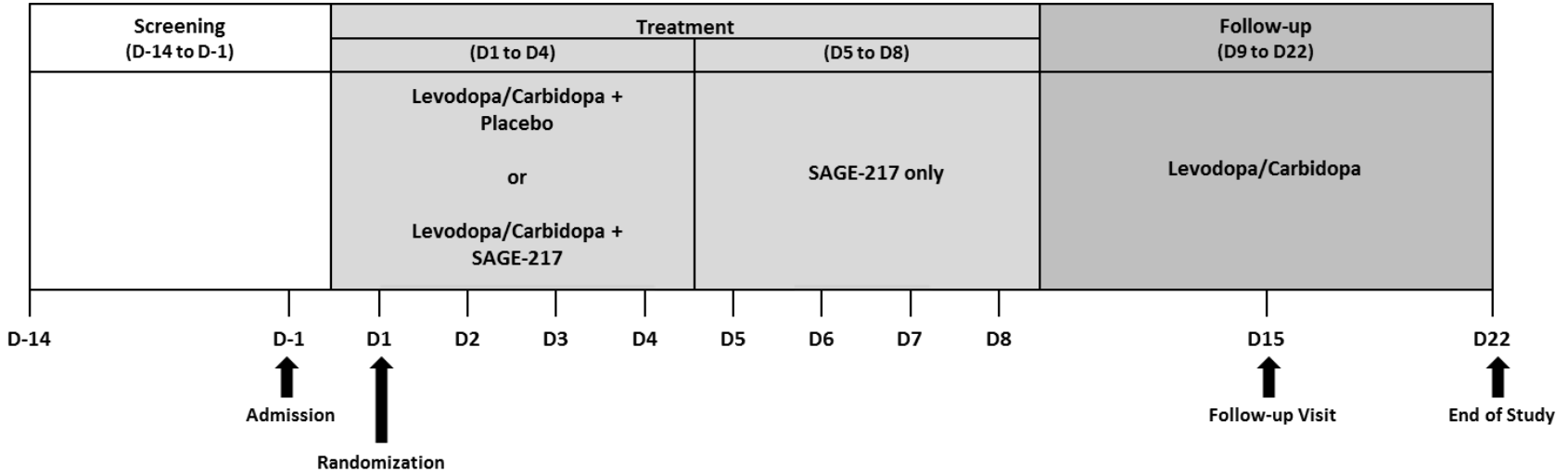
Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons, including the occurrence of adverse events or other findings suggesting unacceptable risk to subjects, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their Institutional Review Board (IRB) and initiate withdrawal procedures for participating subjects.

Figure 1: Study Design of Part A



NOTE: In order to qualify for Part B of the study, a subject must tolerate a dose of at least 10 mg of SAGE-217 Oral Solution in Part A.

Figure 2: Study Design of Part B



NOTE: Part B will be initiated only after review of the Part A interim analysis (after 10 subjects have completed Part A).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

It is anticipated that up to 18 subjects will be enrolled in Part A at up to 4 study centers. All of the following inclusion and exclusion criteria will be applied during screening for Part A, with some of the criteria applied during screening for Part B, as indicated.

8.1. Subject Inclusion Criteria

Subjects must meet the following inclusion criteria for enrollment in the study:

1. Subject has signed an informed consent form (ICF) before any study-specific procedures are performed.
2. Subject is between 40 and 75 years of age, inclusive.
3. Subject has a diagnosis of idiopathic PD based on modified UK Brain Bank Criteria (modified to allow individuals with a family history of PD) (Hughes 1992; Appendix 1).
4. Subjects with PD with a duration of less than 7 years and must meet the criteria for Hoehn and Yahr stage 2 or stage 3 (Appendix 2).
5. Subject has a stable dose of antiparkinsonian agents including immediate-release oral Levodopa or Carbidopa-Levodopa (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.
6. Subject is willing to discontinue his/her treatment with immediate-release oral Levodopa or Carbidopa-Levodopa for at least 8 hours prior to dosing with SAGE-217. (Part B also)
7. Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) or amantadine at least 5 days prior to the day of admission (Day -1). (Part B also)
8. Subjects taking an antidepressant drug, sleep medication, or neuroleptic must have been on a stable dose for at least 1 month prior to the baseline visit.
9. Subjects must have a MoCA score of >22.
10. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests. (Part B also)
11. Female subjects must agree to practice a highly effective method of birth control while on study, and for 30 days after receiving the last dose of study drug. Highly effective methods of birth control include combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, or sexual abstinence. (Part B also)
12. Male subjects must agree to practice a highly effective method of birth control while on study, and for 13 weeks after receiving the last dose of study drug. Effective methods of birth control include sexual abstinence, vasectomy, or a condom with spermicide (men) in combination with female partner's highly effective method. (Part B also)

13. Males must be willing to abstain from sperm donation and females from donating eggs while on study through 13 weeks after receiving the last dose of study drug. (Part B also)

8.2. Subject Exclusion Criteria

Subjects who met any of the following exclusion criteria will be excluded from the study:

1. Subjects with a known hypersensitivity to SAGE-217 Oral Solution or its major excipient, HPβCD. (Part B also)
2. Subjects with early PD (Hoehn and Yahr stage 1) or advanced PD (Hoehn and Yahr stage 4 or stage 5).
3. Subjects with any medical or psychiatric condition that jeopardizes/compromises his/her ability for participation. This includes schizophrenia spectrum and other psychotic disorders, substance-related and addictive disorders, feeding and eating disorders, bipolar and related disorders, structural brain disease including but not limited to history of encephalitis or hydrocephalus and history of clinically significant stroke, or anticipating starting psychotherapy or behavior therapy during the course of the study, or who started psychotherapy or behavior therapy within 30 days prior to Part A Day 1.
4. Subjects with a history of:
    a. Electroconvulsive therapy;
    b. Stereotaxic brain surgery (deep brain stimulation) for PD;
    c. History of suicide attempt within 2 years, or has answered YES to questions 3, 4, or 5 on the C-SSRS at the screening or Day -1 visits, or has current suicidal ideation; or
    d. Impulse control disorder.
5. Subjects with severe depression as defined by a BDI-II score >19.
6. Subjects with Type I or Type II diabetes mellitus.
7. Subjects with presence of drug-induced parkinsonism (eg, metoclopramide, flunarizine), metabolic identified neurogenetic disorders (eg, Wilson's disease), encephalitis, or other atypical Parkinsonian syndromes (eg, progressive supranuclear palsy, multiple system atrophy). (Part B also)
8. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease. (Part B also)
9. Subject has clinically significant abnormal physical examination OR 12-lead ECG at the screening or admission visits. NOTE: QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study. ECG may be repeated once if initial values obtained are outside the specified limits. (Part B also)
10. Subject has a history, presence and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies 1 and 2.

11. Subject has exposure to another investigational medication or device within the prior 30 days.
12. Subject has donated one or more units of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing (1 unit = 450 mL). (Part B also)
13. Subject is unwilling or unable to comply with study procedures. (Part B also)
14. Subject has used any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug. (Part B also)

8.3. Entrance Criteria for Part B

In addition to the inclusion and exclusion criteria determined at screening for Part B indicated in Section 8.1 and Section 8.2, respectively, subjects must be able to tolerate at least 10 mg of SAGE-217 in Part A in order to be enrolled into Part B. Part B will not be initiated until results of the Part A interim analysis have been reviewed.

8.4. Subject Withdrawal Criteria

Participation in the study is strictly voluntary. Subjects are free to discontinue the study at any time without giving their reason(s).

A subject must be withdrawn from the study treatment in the event of any of the following:

- Withdrawal of the subject's consent;
- New onset of a condition that would have met exclusion criterion, is clinically relevant and affects the subject's safety, and discontinuation is considered necessary by the Investigators and/Sponsor;
- Occurrence of intolerable adverse events;
- Occurrence of pregnancy;
- Intake of nonpermitted concomitant medication;
- Subject noncompliance;
- Significant protocol deviation determined in consultation with the Medical Monitor.

If a subject fails to attend scheduled assessments during the course of the study, the Investigators must determine the reasons and the circumstances as completely and accurately as possible and document this in the subject's source documents.

Subjects may be withdrawn from the study if there is concern for the subject's safety or it is determined that the subject is no longer a qualified participant. Any subject who is withdrawn from the study for any reason is to have the final visit assessments performed.

Subjects who withdraw or are withdrawn from the study may be replaced.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol.

9.1.1. Part A

Subjects participating in Part A of the study will take study drug (SAGE-217) in an open-label manner. 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 the following 3 days (Days 1 to 3). On the morning of Day 4, subjects will stop their immediate-release oral Levodopa and take SAGE-217 for 4 days (Days 4 to 7) in the AM with food. On Day 4, subjects will receive a 30 mg dose of SAGE-217. Subjects not tolerating 30 mg will receive 20 mg the next day, and subjects not tolerating 20 mg will receive 10 mg the next day. The dose received on Day 7 will be defined as the tolerated dose for that subject, with this dose to be used as the starting dose for Part B for that subject.

Subjects not tolerating 10 mg will not be able to continue in the study and may be replaced. Levodopa treatment will be resumed on Day 8 and continue through Day 14.

9.1.2. Part B

In order to qualify for Part B of the study, a subject must tolerate a dose of at least 10 mg of SAGE-217 Oral Solution. On Day 1 of Part B, subjects will be randomized in a 1:1 manner to open-label Levodopa plus blinded SAGE-217 Oral Solution or placebo.

- Subjects randomized to the Levodopa plus placebo arm will receive Levodopa plus SAGE-217 matching placebo oral solution in the AM for the first 4 days (Days 1 to 4).
- Subjects randomized to the Levodopa plus SAGE-217 Oral Solution arm 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.

9.2. Concomitant Medications

9.2.1. Prior/Concomitant Medications

Any concomitant medication determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study under the guidance outlined in Section 9.2.

Record the name, start date (if known), indication for use and whether ongoing or stopped of medications/treatments taken within 2 weeks prior to study entry as well as any medications taken during the study.

The charts of all study participants will be reviewed for new concomitant medications through discharge from the unit. Chart reviews will include examination of nursing and physician progress notes, vital signs, and medication records in order to identify adverse events that may be associated with new concomitant medications. New concomitant medications, ongoing concomitant medications with a change in dose, and medical procedures ordered (eg, laboratory assessments, computed tomography or magnetic resonance imaging scans) will be reviewed to determine if they are associated with an adverse event not previously identified.

The Investigator will document all doses of Levodopa and Carbidopa-Levodopa taken by the subject and the use of rescue medication.

9.2.2. Prohibited Medications

Subjects who have used any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug are to be excluded from the study; these medications/products are prohibited during the study.

The anticholinergic drug classes listed in Appendix 3 and amantadine are not permitted in the 5 days prior to the admission visit (Day -1) of each part of the study. The list provides non-exhaustive examples of each drug class.

9.3. Treatment Compliance

Study drug (SAGE-217 or matched placebo) will be prepared by the site pharmacist. All doses of study drug will be administered by site staff while the subject is confined to the clinical unit. The Investigator(s) or designee will record the time and dose of study drug administration in the source documents. Any reasons for noncompliance will also be documented, including:

- Missing visits;
- Interruptions in the schedule of administration; and
- Nonpermitted medications.

The time at which study procedures are conducted should follow the protocol timelines as closely as possible.

9.4. Randomization and Blinding

Part A of the study is open-label.

In 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 groups: open-label Levodopa plus blinded SAGE-217 Oral Solution or matching placebo oral solution. Subjects, clinicians, and the study team will be blinded to treatment allocation. The pharmacist, who will prepare the oral solutions 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.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dosages. The 6 mg/mL stock SAGE-217 Oral Solution will be compounded from SAGE-217 Drug Substance Powder in the Bottle and Excipient(s) in the Bottle (manufactured under current Good Manufacturing Practice [GMP] conditions [redacted]) and further admixed at the clinical site in preparation for dosing. Placebo will be matched to SAGE-217 study drug. Detailed instructions for study drug preparation will be provided in the Pharmacy Manual.

The Sponsor will not provide Levodopa or Carbidopa-Levodopa during the study; subjects will use their prescribed Levodopa or Carbidopa-Levodopa.

10.2. Study Drug Packaging and Labeling

The composition and pharmaceutical quality of the investigational product will be maintained according to the current GMP and Good Clinical Practice (GCP) guidelines and available for review in the study medication documentation. Study drug will be provided to the site as powder in the bottle and excipient(s) in the bottle units to be compounded in the pharmacy at a volume of 125 mL of a 6 mg/mL stock solution and then further diluted to approximately 40 mL at the identified doses. Study drug labels with all required information and conforming to all applicable Code of Federal Regulations and GMP/GCP guidelines will be prepared by the clinical research organization.

10.3. Study Drug Storage

Upon receipt of study drug (SAGE-217 Oral Solution and placebo oral solution), the Investigator or designee will inspect the materials and complete and return the acknowledgment of receipt form enclosed with the parcel. A copy of the signed receipt will be kept in the study files.

The study drug materials for SAGE-217 Oral Solution and placebo oral solution must be carefully stored at the temperature specified in the Pharmacy Manual (eg, clinical dosing solutions stored at approximately 2 to 8°C for 11 days with 24 hours of room temperature excursions allowed after preparation), safely and separately from other drugs. The study drug may not be used for any purpose other than the present study. After the study is completed, all unused study drug must be retained, returned as directed, or destroyed on site per the Sponsor's instructions.

The Investigator or designee will be responsible for ensuring appropriate storage, compounding, dispensing, inventory, and accountability of all clinical supplies. An accurate, timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory must be available for inspection by the designated representatives of the Sponsor or the Sponsor's representatives on request, and must include the information below:

- The identification of the subject to whom the drug was dispensed;

- The date(s) and quantity of the drug dispensed to the subject; and
- The product lot/batch number.

The preparation of the study drugs must be documented on a 'Drug Preparation and Dispensing Log Form' or similar form.

A copy of the inventory record and a record of any clinical supplies that have been destroyed must be documented. This documentation must include at least the information below or as agreed with the Sponsor:

- The number of prepared units;
- The number of administered units;
- The number of unused units;
- The number of units destroyed at the end of the study;
- The date, method, and location of destruction.

10.4. Study Drug Preparation

Each bottle of SAGE-217 Oral Solution 6 mg/mL will be compounded at the clinical pharmacy from components manufactured [redacted] and supplied by the Sponsor per the directions provided in the Pharmacy Manual. The batch formula for a 125 mL solution of the 6 mg/mL stock solution is shown in Table 5.

Table 5: Batch Formula for 125 mL of Stock SAGE-217 Oral Solution 6 mg/mL

Ingredient	Compendia Specification	Concentration (mg/mL)	Amount (mg/Bottle)
SAGE-217	not applicable	6	750
HPβCD [redacted]	USP/EP	457	57,100
Sucralose	USP/NF	0.025	3.124
Water for Injection	USP	not applicable	85,650

Abbreviations: EP = European Pharmacopeia; HPβCD = hydroxypropyl-β-cyclodextrin; NF = National Formulary; USP = United States Pharmacopeia

Additional excipients may be utilized in placebo to match the taste of SAGE-217 Oral Solution. They include sucrose octaacetate, tannic acid, and ammonium glycyrrhizate. The quantities may vary depending on the dose of SAGE-217.

10.5. Administration

SAGE-217 Oral Solution or matching placebo will be administered in the morning with food.

Doses of SAGE-217 and placebo for SAGE-217 will be prepared as an approximate 40 mL oral solution to be swallowed all at once, followed by approximately 200 mL of water that has been used to rinse the dosing bottle. The start time of swallowing the approximately 40 mL oral solution is time zero for all assessments. Subjects may have assistance from the clinic staff when taking the study drug.

During Confinement, each subject's antiparkinsonian agents, including Levodopa or Carbidopa-Levodopa, will be administered by site personnel according to the site's standard operating procedures.

10.6. Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator or designee must maintain a record of all study drug received, used, and discarded. It must be clear from the records which subject received which dose of active or placebo treatment.

The Sponsor will be permitted access to the study supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation. Only unblinded personnel will be able to access the study drug and accountability documentation from first dosing through database hard lock.

The Investigator will document all doses of Levodopa or Carbidopa-Levodopa taken by the subject, including rescue doses.

10.7. Study Drug Handling and Disposal

The pharmacist or designee for drug accountability is to document the date and time of initial compounding, subsequent admixture of dosing solutions, administration of study drug, and for which subject the study drug was intended (ie, record subject initials and birth date or other unique identifier).

At the end of the study, any unused study drug will be retained or returned to the Sponsor for destruction or destroyed locally per the Sponsor's directions; disposition of study drug will be documented.

11. ASSESSMENT OF EFFICACY

Efficacy assessments include evaluation of PD symptoms by the MDS-UPDRS, [redacted] Assessments will be perfo1med periodicall y dming the study as outlined in the Schedule of Events (Table 2 and Table 3).

11.1. Movement Disorder Society- Unified Parkinson's Disease Rating Scale

The UPDRS is the most commonly used scale in clinical studies of PD (Ramaker 2002). In 2007, the MDS revised the scale, which was known as the MDS-UPDRS (Goetz 2007), and subsequently demonstrated the validity of the MDS-UPDRS for rating PD (Goetz 2008). The modified UPDRS includes four scales, with various subscales. Each item is rated from 0 (no1m al) to 4 (severe) (Table 6). The four MDS-UPDRS scalesare:

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

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

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

Pait IV: Motor complications (6 items)

Table 6: Rating Scale for the MDS-UPDRS

Rating	Description
0 = no1mal	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

Several questions in Pait I and all questions in Pait II can be answered by the patient/caregiver and completed without the Investigator's input. The remaining questions in Pait I that deal with complex behaviors, the objective assessments of parkinsonism (Pait III), and the questions that deal with motor fluctuations and dyskinesias (Pait IV) ai·e co m pleted by In vestigato r in terview. Th e tim e requ ired fo r ad m inistering the MDS-UPDRS is estimated to be less than 10 minutes for the interview items of Pait I, 15 minutes for Pait III, and 5 minutes for Paii IV (Goetz 2008).
The complete MDS-UPDRS is to be administered in Pait A at screening, Admission (Day -1), predose on Days 1, 2, 3, and 4; postdose on Day 7; and on Day 14. The complete MDS-UPDRS is to be administered in Pait B at screening, Admission (Day -1), predoseon Days 1 and 4; postdose on Day 8; and on Days 15 and 22.

Pait III of the MDS-UPDRS 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, global spontaneity of movement (Goetz. 2008). Pait III of the MDS-UPDRS (motor examination) is to be completed in Part A at 2, 4, 8, and 12 hours postdose on Days 5, 6, and 8, and in Pait B at 2, 4, 8, and 12 homs postdose on Days 2, 3, 5, 6, 7, and 9. MDS-UPDRS is to be assessed within ±10 minutes of the scheduled times through the 4-hour time point and within ±15 minutes of the scheduled times for the 6-hour through 12-hour time points. The MDS-UPDRS is provided in Appendix 4.

11.2. Exploratory Endpoints

[redacted]

[redacted]

12. PHARMACOKINETICS

12.1. Blood Sample Collection

In Part A, plasma samples for PK analysis will be collected predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Day 4; predose on Day 5 and Day 6; predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Day 7; in AM of Day 8; and Day 14. In Part B, plasma samples for PK analysis will be collected predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Days 1 to 4; 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 the AM on Day 9; and on Days 15 and 22. The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. Samples are to be collected within ±5 minutes of the scheduled sampling time. The Investigator or designee will arrange to have the plasma samples processed, stored, and transported as directed for bioanalysis.

An additional PK sample may be collected at any time if clinically indicated and at the discretion of the Investigator (eg, for unusual or severe adverse events).

Each sample will be marked with unique identifiers such as the study number, subject number, and the nominal sample time. The date and actual time that the blood sample was taken will be recorded on the eCRF or electronically with a bar code or other method.

12.2. Storage and Shipment of Pharmacokinetic Samples

The plasma samples should be kept frozen at approximately -70°C to -80°C until analyzed. They should be packed as directed to avoid breakage during transit and with sufficient dry ice to prevent thawing for at least 72 hours. A specimen-identification form must be completed and sent to the laboratory with each set of samples. The clinical site will arrange to have the plasma samples transported as directed for bioanalysis as detailed in the PK instructions.

12.3. Sample Analysis

Bioanalysis of plasma samples for the determination of concentrations of SAGE-217 and possibly SAGE-217 metabolites will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory. Pharmacokinetic parameters will be derived such as area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), the distributional half-life and terminal half-life ($t_{1/2}$), and steady-state drug concentration in the plasma (C_{ss}).

13. ASSESSMENT OF SAFETY

13.1. Safety and Tolerability Parameters

Safety and tolerability of study drug will be evaluated by adverse event reporting, vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, and SSS and MOAA/S scores.

13.1.1. Demographic/Medical History

Age, gender, race, and ethnic origin will be recorded at the Screening visit for Part A. A full medical history, including PD history (eg, time of diagnosis, staging) and medication history, will be recorded at the Screening visit for Part A and updated, as needed, as screening for Part B.

13.1.2. Vital Signs

Vital signs comprise respiratory rate, temperature, and supine (supine for at least 5 minutes prior to the measurement) and standing systolic and diastolic blood pressure and heart rate.

In Part A, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in AM of Day 8; and on Day 14. In Part B, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 8; in AM on Day 9; and on Days 15 and 22. Vital signs and pulse oximetry are to be assessed within ±10 minutes of the scheduled times through the 4-hour time point and within ±15 minutes of the scheduled times for the 6-hour through 16-hour time points.

13.1.3. Weight and Height

Body weight and height will be measured at the Screening visits for Parts A and B.

13.1.4. Physical Examination

A physical examination of all major body systems will be undertaken and recorded at the Screening visits for Parts A and B. Symptom-directed physical examinations will be performed during Part A on Admission (Day -1), Day 1, Day 3, Day 4, Day 6, and Day 8. Symptom-directed physical examinations will be performed during Part B on Admission (Day -1), Day 1, Day 3, Day 4, Day 5, Day 7, Day 8, Day 9, and Day 15.

13.1.5. Electrocardiogram (ECG)

A supine 12-lead ECG will be performed at the times specified below and the standard intervals recorded as well as any abnormalities.

In Part A, the 12-lead ECG will be assessed at screening and Admission (Day -1); predose on Days 1 and 3; predose and 1 and 12 hours postdose on Days 4, 5, 6, and 7; in AM on Day 8; and Day 14. In Part B, the 12-lead ECG will be assessed at screening and Admission (Day -1); predose and 1 and 12 hours postdose on Days 1 through 8; in AM on Day 9; Days 15 and 22.

All time points are relative to the time of dosing. ECGs are to be performed within ±10 minutes of the predose and 1-hour time points and within ±15 minutes of the 12-hour time point.

13.1.6. Laboratory Assessments

In Part A, blood samples will be collected for hematology and serum chemistry at the Screening visit, on Admission (Day -1), predose on Days 4, 6, and 8; and on Day 14. Urine samples will be collected in Part A at screening and Admission (Day -1); predose on Day 4 and Day 7; and on Day 14. In Part B, blood samples will be collected at screening and Admission (Day -1); predose on Days 1, 3, 4, 5, 6, and 8; on Day 9 and Day 15. Urine samples will be collected in Part B at screening and Admission (Day -1); predose on Day 4 and Day 8; and on Day 15.

Serum and urine samples for pregnancy tests (females only) will also be collected. These assessments should be performed in accordance with the Schedule of Events (Table 2 and Table 3) and as outlined individually below.

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS). Screening results considered abnormal, CS recorded at the Screening visit may make the subject ineligible for the study pending review by the Medical Monitor. Clinical laboratory results that are abnormal, CS during the study but within normal range at baseline and/or indicate a worsening from baseline will be considered adverse events, assessed according to Section 13.2, and recorded in the eCRF.

13.1.6.1. Hematology

Hematology tests will include complete blood count (CBC), including red blood cells, white blood cells with differentiation, hemoglobin, hematocrit, reticulocytes, and platelets. The coagulation panel will include activated partial thromboplastin time, prothrombin time, and international normalized ratio.

13.1.6.2. Blood Chemistry

Serum chemistry tests will include serum electrolytes, renal function tests, including creatinine, blood urea nitrogen, bicarbonate or total carbon dioxide, liver function tests, including total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), total protein, and albumin.

13.1.6.3. Urinalysis

Urinalysis will include assessment of protein, blood, glucose, ketones, bile, urobilinogen, hemoglobin, leukocyte esterase, nitrites, color, turbidity, pH, and specific gravity.

13.1.6.4. Virus Serology

Subjects will be screened for hepatitis (HBsAg and anti-HCV) and HIV prior to being enrolled in the study.

13.1.6.5. Pregnancy Screen

Females of childbearing potential will be tested for pregnancy at Parts A and B by serum pregnancy test at the Screening visits and by urine pregnancy test on Day -1 (Admissions).

13.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS)

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

If in the opinion of the Investigator, the subject is showing any suicidal tendency, no further study drug will be administered and the subject will be referred to a psychologist or psychiatrist for further evaluation. This information will be tracked.

The "Baseline/Screening" C-SSRS form will be completed on Screening of Part A (lifetime history and past 24 months). In Part A, the "Since Last Visit" C-SSRS form will be completed on Admission (Day -1); 12 hours postdose on Days 1, 2, and 3; predose on Days 4, 5, 6, and 7; and on Days 8 and 14. In Part B, the "Since Last Visit" C-SSRS form will be completed on Admission (Day -1); 12 hours postdose on Day 1 through Day 8; and on Days 9, 15, and 22. The C SSRS is provided in Appendix 9.

13.1.8. Stanford Sleepiness Scale (SSS)

The SSS is 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'.

In Part A, the SSS will be administered on Admission (Day -1); predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in the AM on Day 8; and Day 14. All time points are relative to the time of dosing. 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. In Part B, the SSS will be administered on Admission (Day -1); predose on Days 1 through 8; in AM on Day 9; and Days 15 and 22. The SSS should be performed prior to the MOAA/S score. The SSS is provided in Appendix 10.

13.1.9. Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S)

The MOAA/S allows exploration of deeper sedation states than the SSS. If an 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. In Part A, the MOAA/S assessment should be conducted after other assessments that are scheduled at the same time point. In Part A, the MOAA/S will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 3, 4, 5, 6, and 7; in AM on Day 8; and Day 14. In Part B, the MOAA/S will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 8; in AM on on Day 9; and Days 15 and 22. The MOAA/S 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 for the 6-hour through 16-hour time points. The MOAA/S is provided in Appendix 11.

13.2. Adverse and Serious Adverse Events

Adverse events will be collected after the ICF has been signed. Medical conditions that occur after the ICF has been signed will be captured on the adverse event eCRF.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (version 18.1 or higher).

13.2.1. Definition of Adverse Events

13.2.1.1. Adverse Event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an adverse event can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All adverse events that occur after any subject has been enrolled, before treatment, during treatment, or following the cessation of treatment until the Day 22 Follow-up visit of Part B, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics.

13.2.1.2. Suspected Adverse Reaction

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

13.2.1.3. Serious Adverse Event

A serious adverse event is an adverse event occurring during any study phase and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- It results in death
- It is immediately life-threatening
- It requires inpatient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- It results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

All serious adverse events that occur after any subject has been enrolled, before treatment, during treatment, and until the Day 22 Follow-up visit of Part B, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics.

13.2.1.4. Recording Sedation as an Adverse Event

Sedation will be assessed using protocol-specified rating scales. In order to standardize the reporting of sedation as adverse events, Investigators must record sedation as an adverse event if there is a score of >5 on the SSS and/or a score of ≤2 on the MOAA/S. Consideration should be given to the most appropriate term to describe the sedation characteristics.

13.2.2. Pregnancy

Any pregnancy occurring during this study will be reported within 24 hours of notification of the Investigator. The Investigator will promptly notify the Medical Monitor and withdraw the subject from the study. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The Investigator should request permission to contact the subject, the subject's spouse/partner (if the subject is male and his spouse/partner becomes pregnant) or the obstetrician for information about the outcome of the pregnancy (spontaneous miscarriage, elective termination, live birth), and in the case of a live birth, about any congenital abnormalities. If a congenital abnormality is reported, then it should be recorded in the source documents and reported as a serious adverse event. Spontaneous miscarriages should also be reported and handled as serious adverse events. Elective abortions without complications should not be handled as adverse events.

13.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each adverse event (unrelated, possibly related or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the adverse event should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the adverse event, then the adverse event should be considered "related."

Not related	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possibly related	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.
Probably related	The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.

If the relationship between the adverse event/serious adverse event and the investigational product is determined to be "possible" or "probable", the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

13.4. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as adverse events unless they prompt corrective medical action by the Investigator, constitute a serious adverse event or lead to discontinuation of administration of study drug.

Information about adverse events will be collected from the signing of the ICF until the final visit of the study for that subject. Adverse events that occur after the first administration of study drug will be denoted TEAEs.

All adverse events will be followed until they are resolved or have reached a clinical plateau with no expectation of future change.

The adverse event term should be reported in standard medical terminology when possible. For each adverse event, the Investigator will evaluate and report the onset (date and time), resolution or clinical plateau (date and time), intensity, causality, action taken, outcome, and whether or not it caused the subject to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe adverse events. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.2.1.3. An adverse event of severe intensity may not be considered serious.

13.5. Reporting Serious Adverse Events

All serious adverse events (regardless of causality) will be recorded from the signing of the ICF until the Day 22 Follow-up visit of Part B. Any serious adverse events considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All serious adverse events must be reported to the Sponsor or Sponsor's designee immediately by phone and in writing within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the serious adverse event pages, verify the accuracy of the information recorded on the serious adverse event pages with the corresponding source documents, and send a copy to Sage Therapeutics or designee.

Additional follow-up information, if required or available, should be sent to Sage Therapeutics or designee within 24 hours of receipt; a follow-up serious adverse event form should be completed and placed with the original serious adverse event information and kept with the appropriate section of the CRF and/or study file.

Sage Therapeutics or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB of all serious adverse events that occur at his or her site if applicable per the IRB's requirements. Investigators

will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB of these additional serious adverse events.

14. STATISTICAL METHODS AND CONSIDERATIONS

14.1. Data Analysis Sets

The safety population is defined as all subjects who are administered study diug.

The efficacy population will consist of all subjects in the safety population who receive at least one dose of study drng and have at least one postdose MDS-UPDRS evaluation.

The PK population will consist of all subjects in the safety population with sufficient plasma concentrations for PK evaluations.

Separate populations will be defined for each pa1t of the study.

14.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. No imputation process will be used to estimate missing data. No sensitivity analysis of missing data will be perfo1med.

14.3. Demographics and Baseline Characteristics

Demographics, such as age, gender, race, and ethnicity, and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized.

Categorical summaries, such as gender and race, will be summarized by frequency and percentage. Continuous summaries, such as age, height, weight, BMI, and baseline vital signs, will be summarized using descriptive statistics.

Hepatitis, HIV, and pregnancy screening results will be listed, but not summarized as they are considered pait of the inclusion/exclusion criteria.

Medical histo1y will be listed by subject.

14.4. Efficacy Endpoints

The primary endpoints of this study relate to safety and tolerabilit y. Efficacy assessments include evaluation of PD s n toms b the MDS-UPDRS, [redacted]

14.4.1. Secondary Efficacy Endpoints

In Pait A, changes in the MDS-UPDRS- Pait III score will be summaii·zed overall and by tolerated dose. In Pait B, changes in the MDS-UPDRS - Pa1t III score and the MDS-UPDRS - Paits I-IV total score will be sUllllnai·izedoverall and by randomized treatment sequence and tolerated dose.

14.4.2. Exploratory Efficacy Endpoints

[redacted]

[redacted]

14.5. Safety and Tolerability Analyses

Data from vital signs, clinical laboratory measures, ECG, C-SSRS, SSS, and MOAA/S will be summarized using descriptive statistics by group and time point, where applicable. Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and will be summarized using descriptive statistics. Out-of-range safety endpoints may be categorized as low or high, where applicable. For all categorical endpoints,summaries will include counts and percentages.

14.5.1. Adverse Events

Adverse events will be coded using the MedDRA coding system (version 18.1 or higher). The analysis of adverse events will be based on the concept of TEAEs. A TEAE is defined as an adverse event with onset after the start of open-label study drng, or any worsening of a pre-existing medical condition/adverse event with onset after the staii of open-label study chu g and until 14 days after the last dose. The incidence of TEAEs will be summarized overall and by MedDRA System Organ Class, preferred tenn, and dose group. Incidences will be presented in order of decreasing frequency. In addition, summaii·es will be provided by maximum severity (see Section 13.4) and relationship to study chu g (see Section 13.3).

Treatment-emergent adverse events leading to discontinuation and serious adverse events (see Section 13.2.1.3 for definition) with onset after the first dose of open-label study chu g w ill also be summaii·zed.

All adverse events and serious adverse events (including those with onset or worsening before the staii of open-label study chu g) thro ugh the Day 22 Follow-up visit of Paii B will be listed.

14.5.2. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from baseline of Paii A and Paii B in vital signs will be evaluated by time point.

14.5.3. Physical Examinations

Screening physical examination results for Pali A and Paii B will be listed by subject. Any clinically significant physical exainination will be recorded in medical histo1y . Physical examination findings will be listed by subject and visit; abno lmal findings will be flagged on the listing.

14.5.4. 12-Lead ECG

The following ECG parameters will be listed for each subject: heart rate, PR, QRS, QT, QTc, and QTcF. Any clinically significant abnormalities or changes in ECGs should be listed as an adverse event. Electrocardiogram findings will be listed by subject and visit.

14.5.5. Clinical Laboratory Evaluations

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline of Parts A and B in clinical laboratory measures will be summarized.

14.5.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality data collected on the C-SSRS will be listed for all subjects. Listings will include behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

14.5.7. Stanford Sleepiness Scale (SSS)

Sedation data collected on the SSS will be listed for all subjects. Changes in score over time will be represented graphically, and change from baseline of Part A and Part B will be summarized.

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

Sedation data collected on the MOAA/S will be listed for all subjects. Changes in score over time will be represented graphically, and change from baseline of Part A and Part B will be summarized.

14.5.9. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and will be coded using World Health Organization (WHO)-Drug dictionary September 2015, or later.

Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those taken during the 4 weeks prior to the date of the first dose of open-label study drug. Concomitant medications are defined as those with a start date on or after the first dose of open-label study drug, or those 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. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Concomitant medications will be assigned to the study part in which they are being taken. 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.

The use of rescue medication will be recorded and summarized.

14.6. Pharmacokinetic Analysis

Phaimacokinetic parameters will be summarized using appropriate descriptive statistics. Time to reach maximum concentration (tma.x) will be sunnnarized using number (n), mean, standai·d deviation, median, minimum, and maximum. All other PK pai·ameters will be Sllilllllarized using n, geometric mean , coefficient of vaii·ation, median, minimum, and maximum and listed by subject.

Wherever necessaiy and appropriate, PK pai·ameters will be dose-adjusted to account for individual differences in dose.

[redacted] Additional exposure-response analyses may be perfo1med for other measures of efficacy and safety.

14.7. Determination of Sample Size

Approximately 18 subjects will be emolled in Pait A. An interim analysis is planned after 10 subjects have completed Pait A through Day 14. Approximately 12 subjects are anticipated to be randomized to Part B. This number of subjects is thought to be sufficient to assess preliminaiy safety and tolerability as well as a signal of efficacy of SAGE-217 Oral Solution in subjects with PD.

14.8. Changes From Protocol Specified Analyses

Any changes from the analytical methods outlined in the protocol will be documented in the final statistical analysis plan.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of <Sponsor> will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sage Therapeutics or designee or its representatives. This will be documented in a Clinical Study Agreement between Sage Therapeutics and the Investigator.

During the study, a monitor from Sage Therapeutics or designee will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s);
- Confirm that facilities remain acceptable;
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts);
- Record and report any protocol deviations not previously sent to Sage Therapeutics or designee; and
- Confirm adverse events and serious adverse events have been properly documented on eCRFs and confirm any serious adverse events have been forwarded to Sage Therapeutics or designee and those serious adverse events that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

15.2. Audits and Inspections

Authorized representatives of Sage Therapeutics, a regulatory authority, an Independent Ethics Committee (IEC) or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sage Therapeutics or designee audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Council on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency about an inspection.

15.3. Institutional Review Board (IRB)

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator and institution will permit study-related monitoring, audits, IRB review, and regulatory inspections as requested by Food and Drug Administration, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (ie, original medical records, laboratory reports, hospital documents, progress reports, signed ICFs) in addition to eCRFs.

Quality assurance and quality-control systems with written standard operating procedures will be followed to ensure this study will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality-assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements made by the Sponsor with the Investigator/institution and any other parties involved with the clinical study will be in writing in a separate agreement.

17. ETHICS

17.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Sage Therapeutics or designee before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Sage Therapeutics or designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

17.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and the most recent amendment (2008) and are consistent with ICH/GCP and other applicable regulatory requirements.

17.3. Written Informed Consent

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject’s signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

18. DATA HANDLING AND RECORDKEEPING

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

Electronic case report forms will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, and subject status.

The Investigator will have access to the electronic data capture system and will receive a copy of the subject eCRF data at the end of the study. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

18.1. Inspection of Records

Sage Therapeutics or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

18.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Sage Therapeutics or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18.3. Confidentiality

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available study registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used

towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

19. PUBLICATION POLICY

All information concerning SAGE-217 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

20. LIST OF REFERENCES

Belelli D, Casula A, Ling A, Lambert JJ. The influence of subunit composition on the interaction of neurosteroids with GABA(A) receptors. Neurophan nacology. 2002 Sep;43(4):651- 61.

[redacted]

Bergman H, Deuschl G. Pathophysiology of Parkinson's disease: from clinical neurology to basic neuroscience and back. Mov Disord. 2002;17:S28-S40.

[redacted]

di Michele F, Longone P, Romeo E, et al. Decreased plasma and cerebrospinal fluid content of neuroactive steroids in Parkinson's disease. Neurol Sci. 2003;24(3):172-3.

Goetz CG, Poewe W, Rascol 0 , et al. Movement Disorder Society Task Force Report on the Hoehn and Yalu Staging Scale: Status and Recommendations. Mov Dis. 2004;19(9):1020- 8.

Goetz CG, Fahn S, Maitinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, fonnat, and clinimetric testing plan. Mov Disord. 2007;22(1):41-4 .

Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Pai·kinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov Disord. 2008;23(15):2129-70.

Hoehn M, Yahr M. Parkinsonism: onset, progression and mo1tality. Neurology. 1967;17(5):427-42.

[redacted]

Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Pai·kinson's disease. A clinico-pathological study of 100 cases. JNNP. 1992;55:181-4.

Jankovic J. Moto r fluctuations and dyskinesia in Parkinson's disease: Clinical manifestations. Mov Disord. 2005;11:ll -6.

Jankovic J. Parkinson's' disease: clinical features and diagnosis. JNNP. 2008;79:368-76.

Kasten M, Brnggemann N, Schmidt A, Klein C. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology. 2010;75 (5):478-9.

[redacted]

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.

Ramaker C, Marinus J, Stiggelbout AM, et al. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. Mov Disord. 2002;17(5):867–76.

Siderowf A, Lang AE. Pre-motor Parkinson's disease; concepts and definitions. Mov. Disord 2012;27, 608-16.

Stern MB. Dopamine agonists modify the course of Parkinson disease. Arch Neurol. 2004;61:1969-71.

Weiner WJ. Initial treatment of Parkinson disease: levodopa or dopamine agonists. Arch Neurol. 2004;61:1966-9.

Winkler C, Bentlage C, Nikkhah G, et al. Intracranial transplants of GABA-rich striatal tissue induce behavioral recovery in the rat Parkinson model and promote the effects obtained by intrastriatal dopaminergic transplants. Exp. Neurol. 1999;155:165-186.

21. APPENDICES

Copies of scales and questionnaires included in the following appendices are for reference only; the rating scales and questionnaires reproduced in the eCRFs are to be used for actual subject assessment per the Schedule of Events.

APPENDIX 1. UNITED KINGDOM BRAIN BANK CRITERIA

UK PARKINSON'S DISEASE SOCIETY BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA*

Step 1. Diagnosis of Parkinsonian Syndrome

- Bradykinesia
- At least one of the following
  - Muscular rigidity
  - 4-6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease

- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

**From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181-184.*

APPENDIX 2. HOEHN AND YAHR STAGING CRITERIA

The Hoehn and Yahr scale, a commonly used system for describing how the symptoms of Parkinson's disease progress, was first published in 1967 (Hoehn 1967). The original scale included 5 disease stages, numbered 1 to 5. The scale was later modified to include two intermediate stages (Goetz 2004).

Original Hoehn and Yahr Scale

Stage 1	Unilateral involvement only, usually with minimal or no functional disability
Stage 2	Bilateral or midline involvement without impairment of balance
Stage 3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent
Stage 4	Severely disabling disease; still able to walk or stand unassisted
Stage 5	Confinement to bed or wheelchair unless aided

Modified Hoehn and Yahr Scale

Stage 0	No signs of disease
Stage 1	Symptoms are very mild; unilateral involvement only
Stage 1.5	Unilateral and axial involvement
Stage 2	Bilateral involvement without impairment of balance
Stage 2.5	Mild bilateral disease with recovery on pull test
Stage 3	Mild to moderate bilateral disease; some postural instability; physically independent
Stage 4	Severe disability; still able to walk or stand unassisted
Stage 5	Wheelchair bound or bedridden unless aided

APPENDIX 3. ANTICHOLINERGIC DRUGS

The following drugs are not permitted in the 5 days prior to receiving the first dose of study drug in Part A and Part B. The list below gives a non-exhaustive list of examples of each drug class.

A. Antimuscarinic agents

Atropine	Benzatropine	Biperiden	Chlorpheniramine
Dicyclomine	Dimenhydrinate	Diphenhydramine	Doxepin
Doxylamine	Glycopyrrolate	Hydroxyzine	Ipratropium
Orphenadrine	Oxitropium	Oxybutynin	Tolterodine
Tiotropium	Trihexyphenidyl	Scopolamine	Solifenacin
Tropicamide			

Tricyclic antidepressants (amitriptyline, clomipramine, doxepin, imipramine, trimipramine, amoxapine, desipramine, nortriptyline, protriptyline)

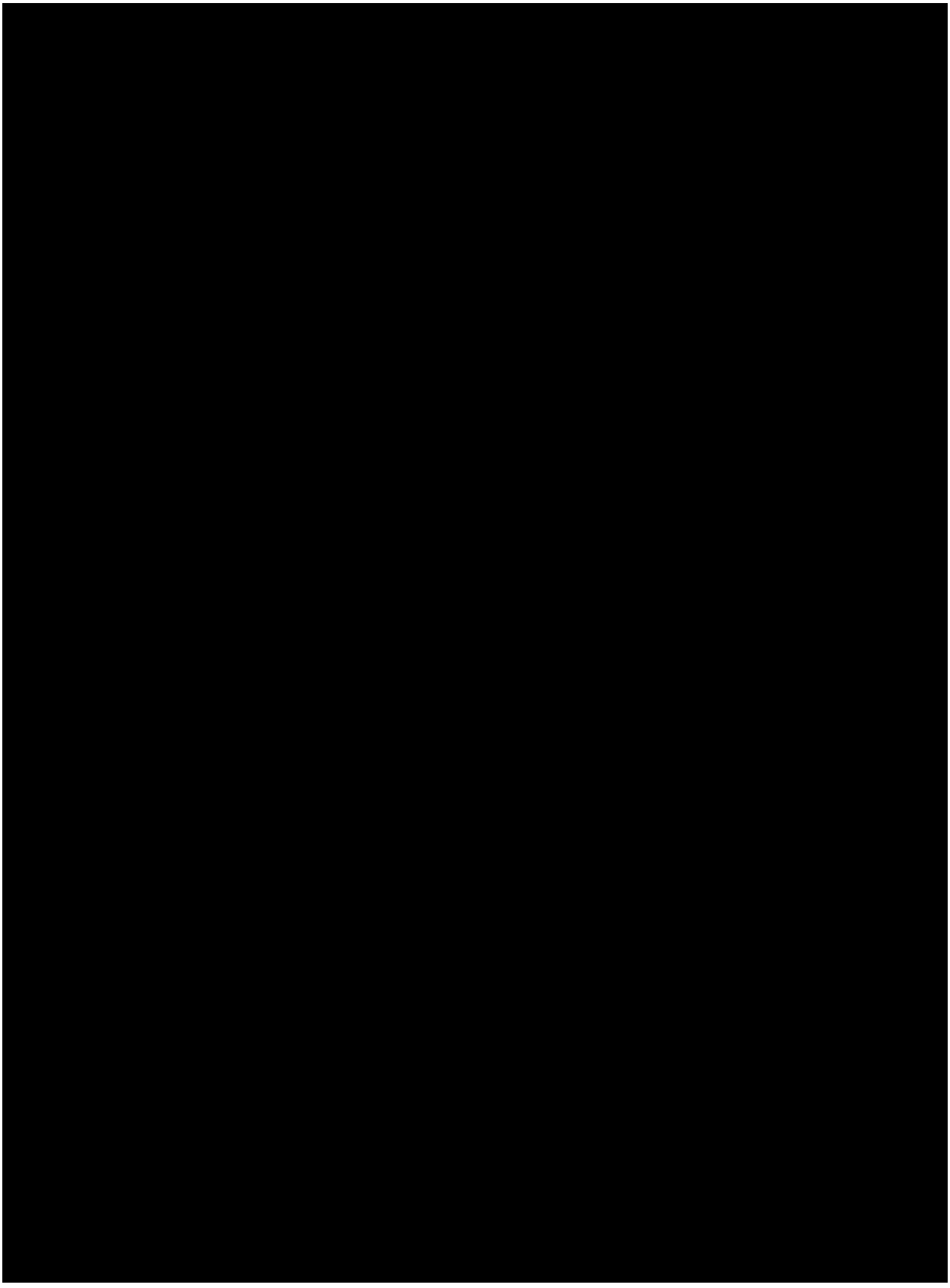
B. Antinicotinic agents:

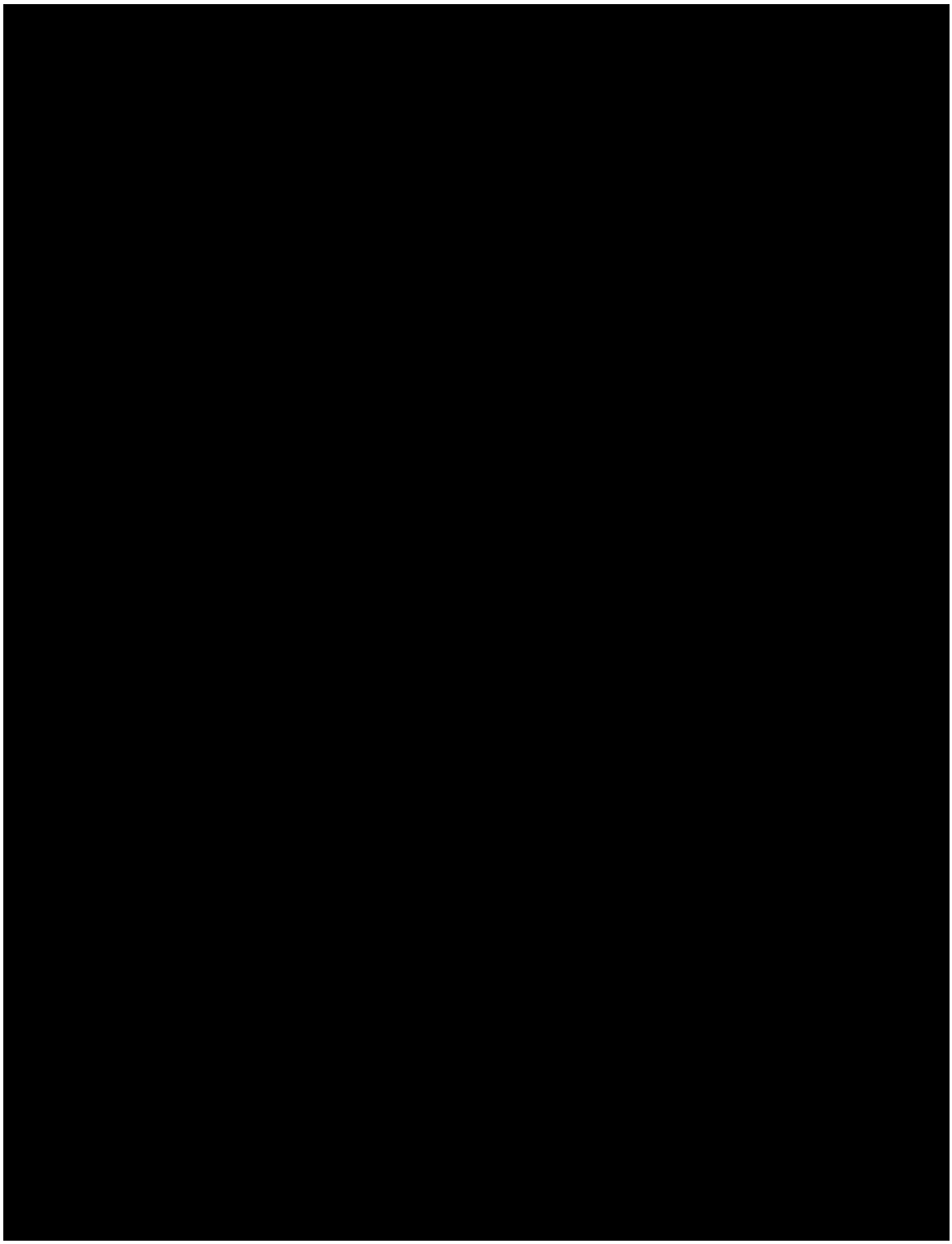
Bupropion	Dextromethorphan	Doxacurium	Hexamethonium
Mecamylamine	Tubocurarine		

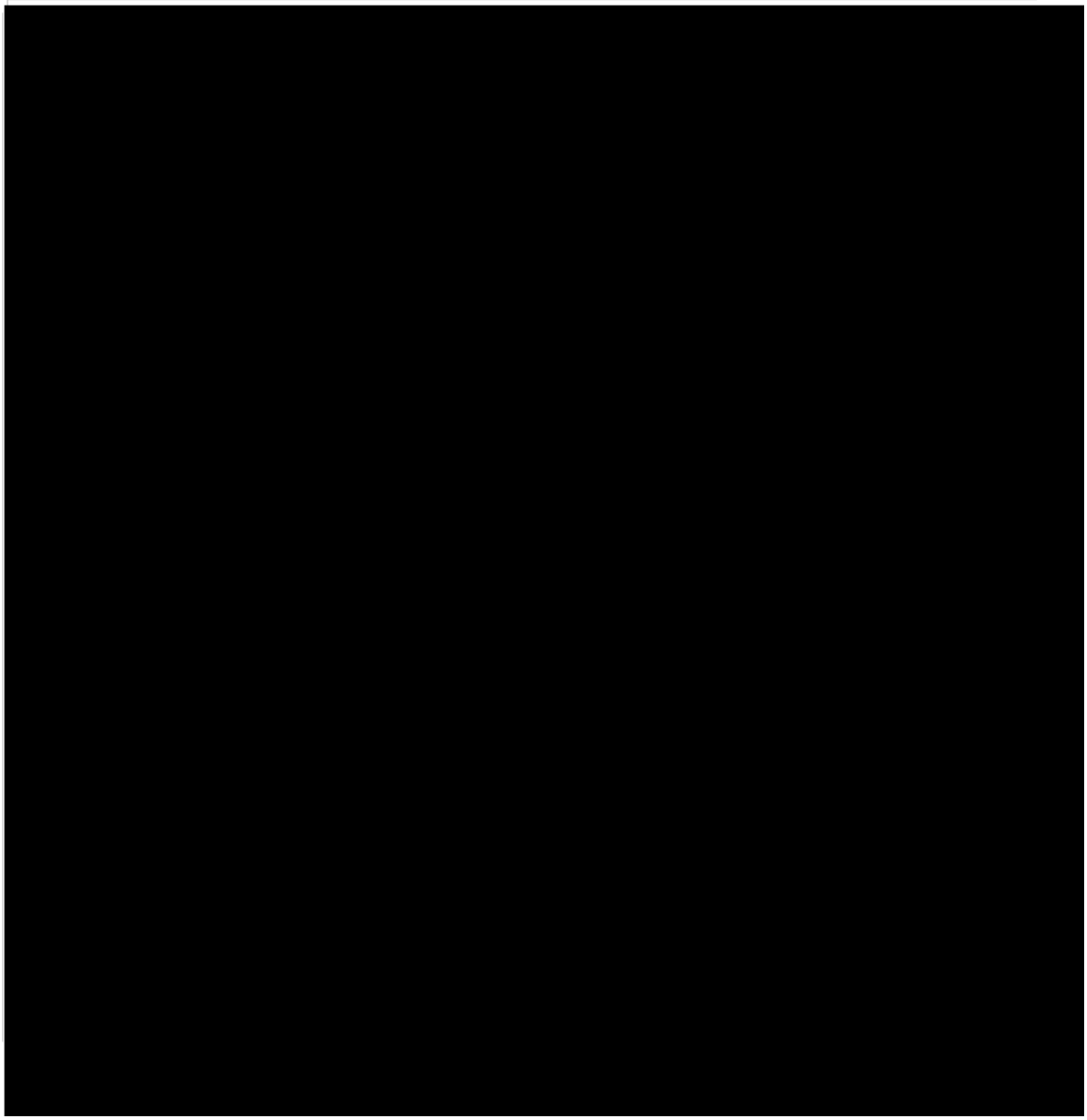
APPENDIX 4. MOVEMENT DISORDER SOCIETY-UNIFIED PARKINSON'S DISEASE RATING SCALE (MDS-UPDRS)

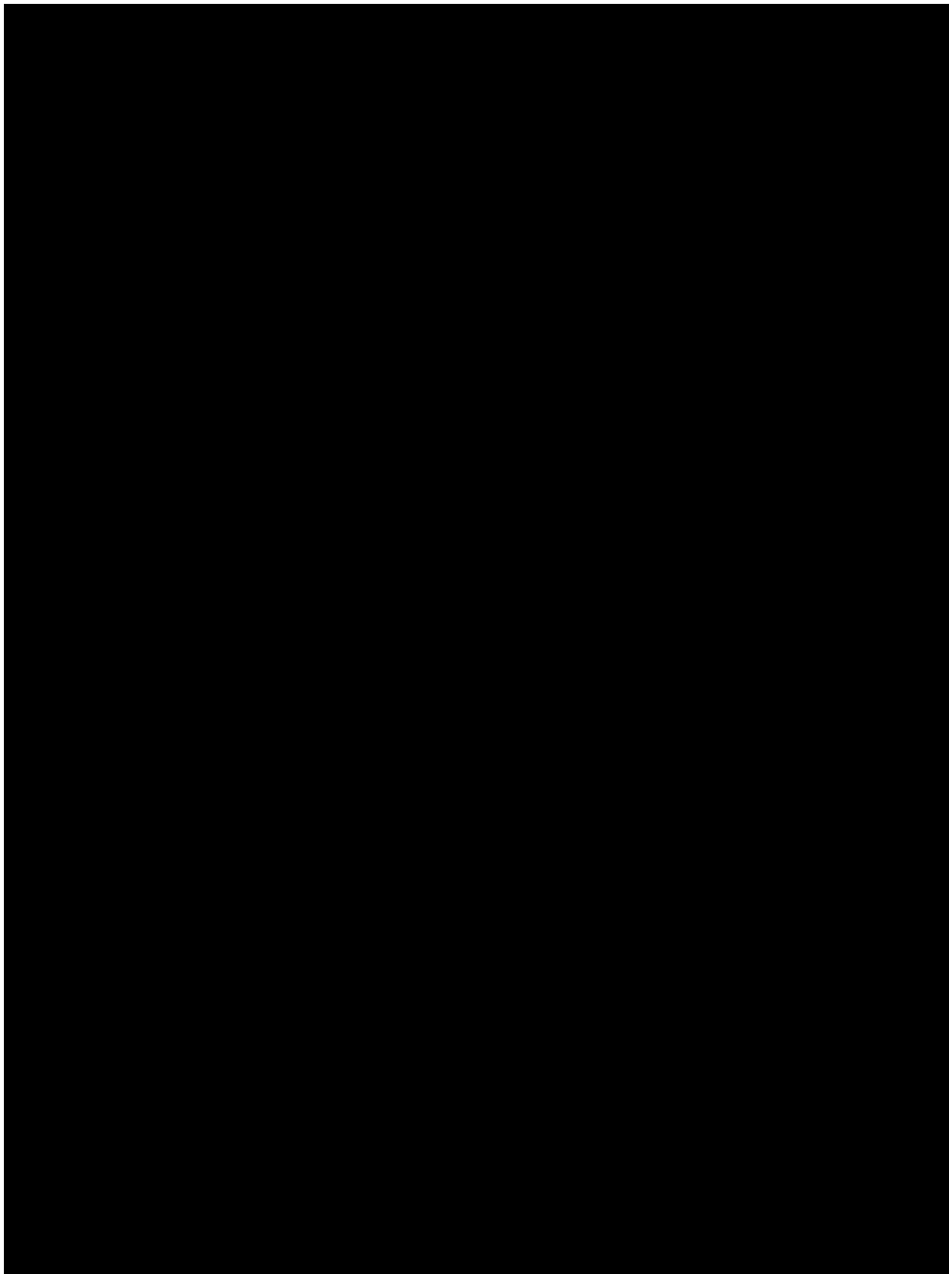
Part I: **NomnotorAspects of Experiences of Daily Living**	**Part** II: **Moto1· E xp e 1·ien ces of Dail y Li vi ng**
Cogniti ve impairmen t	Speech
Hallucinations and psychosis	Saliva and drooling
Depressed mood	Chewing and swallowing
Anxious mood	Eating tasks
Apathy	Dressing
Features of dopamine dysregulation syndrome	Hygiene
Sleep problems	Handwriting
Daytime sleepiness	Doing hobbies and other activities
Pain and other sensations	Turning in bed
Urinary problems	Tremor impact on activities
Constipation problems	Getting in and out of bed
Lightheadedness on standing	Walking and balance
Fatigue	Freezing
Part III: **Motor Examination**	**Part** IV : **Motor Complications**
Speech	Time spent with dyskinesias
Facial expression	Functional impact of dyskinesias
Rigidity **(neck;** right/left upper/lo wer extremities)	Painful *off* state dystonia
Finger tapping (right/left hands)	Time spent in the *off* state
Hand movements (right/left hands)	Functional impact of fluctuations
Pronation-supination movements of right/left hands	Complexity of motor functions
Toe tapping (right/left foot)	
Leg agility (right/left leg)	
Arising from chair	
Gait	
Freezing of gait	
Postural instability	
Posture	
Global spontaneity of movement (body bradykinesia)	
Postural tremor of right/left hands	
Kinetic tremor of right/left hands	
Rest tremor amplitude: right/left upper/lower extremities; lip jaw	
Constancy of rest tremor	

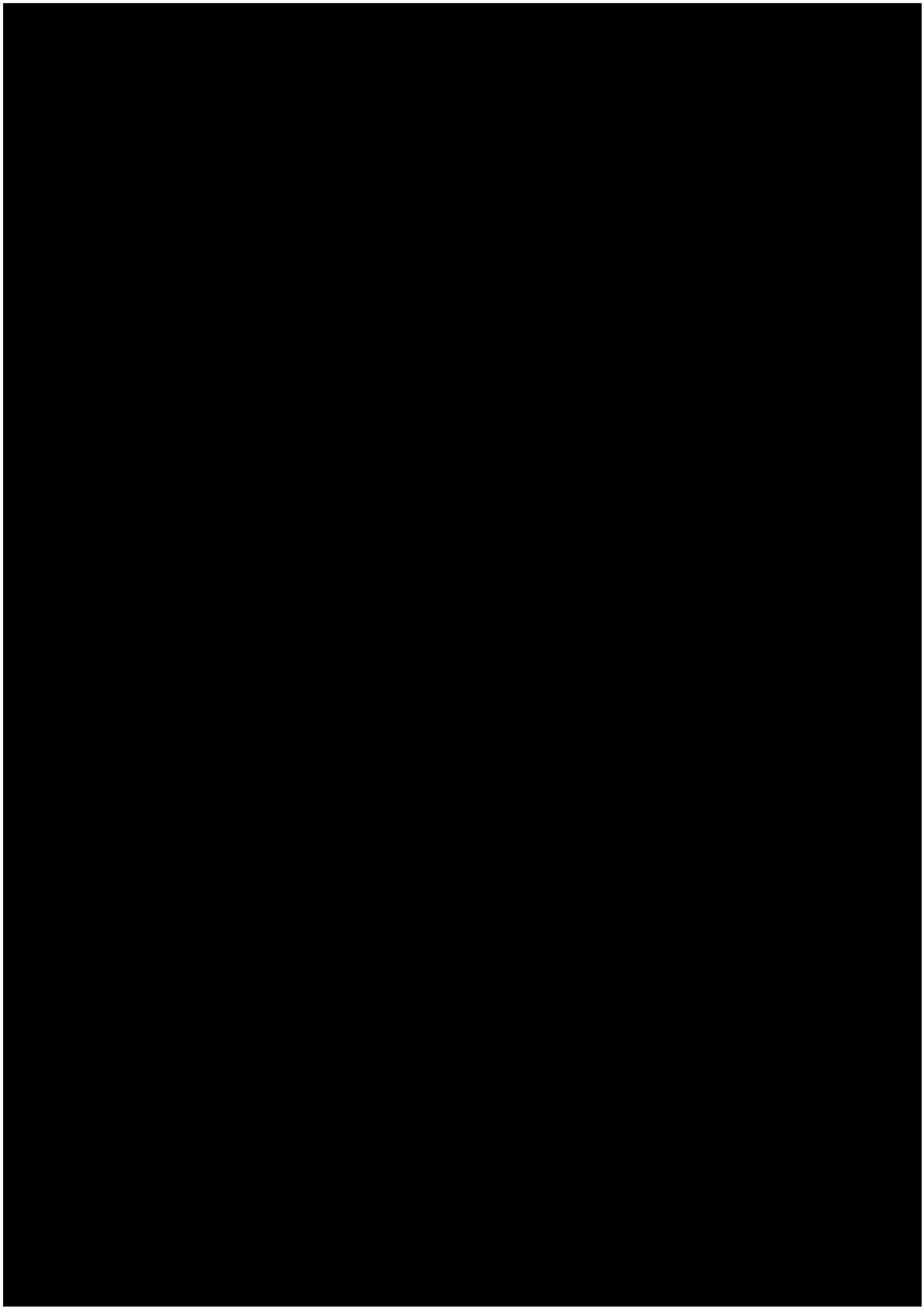
[redacted]

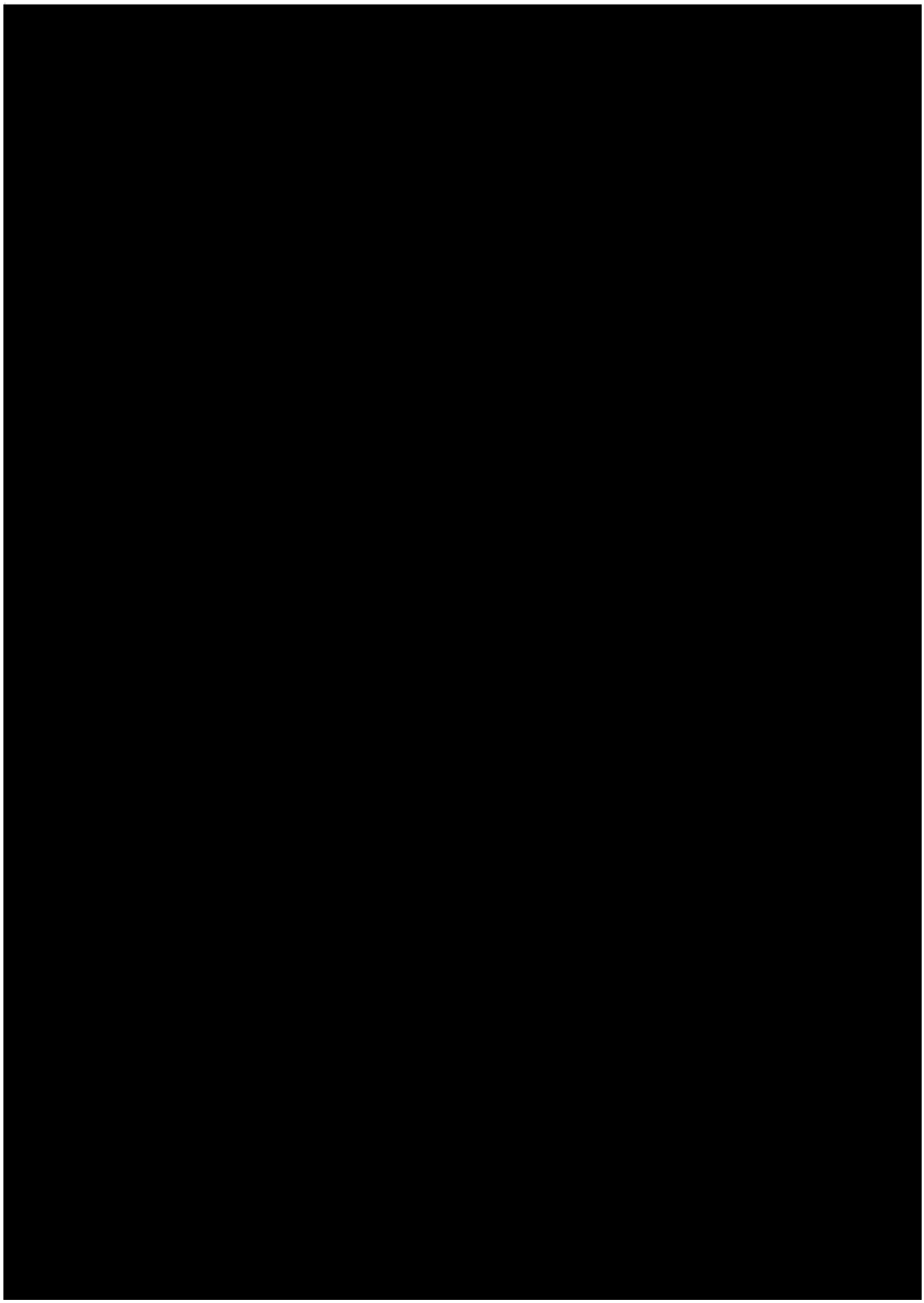












APPENDIX 9. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION AND SINCE LAST VISIT VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. <u>Lifetime</u> - *Most Severe Ideation:* ____ (*Type # (1-5)*) ____ (*Description of Ideation*) <u>Past X Months</u> - *Most Severe Ideation:* ____ (*Type # (1-5)*) ____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	___	___
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	___	___
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	___	___
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	___	___
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	___	

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past__ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes No ☐ ☐ Total # of Attempts ____	Yes No ☐ ☐ Total # of Attempts ____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes No ☐ ☐	Yes No ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of interrupted ____	Yes No ☐ ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes No ☐ ☐ Total # of aborted ____	Yes No ☐ ☐ Total # of aborted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes No ☐ ☐	Yes No ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes No ☐ ☐	Yes No ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____

C-SSRS—Baseline/Screening (Version 1/14/09)
Page 2 of 2

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it....and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Completed Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX 10. STANFORD SLEEPINESS SCALE (SSS)

This is a quick way to assess how alert you are feeling. If it is during the day when you go about your business, ideally you would want a rating of a one. Take into account that most people have two peak times of alertness daily, at about 9 a.m. and 9 p.m. Alertness wanes to its lowest point at around 3 p.m.; after that it begins to build again. Rate your alertness at different times during the day. If you go below a three when you should be feeling alert, this is an indication that you have a serious sleep debt and you need more sleep.

An Introspective Measure of Sleepiness
The Stanford Sleepiness Scale (SSS)

Degree of Sleepiness	**Scale Rating**
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

APPENDIX 11. MODIFIED OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (MOAA/S)

Modified Observer's Assessment of Alertness/Sedation Scale

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Summary of Changes Page
Protocol 217-PRK-201
Date 05 Oct 2016

The following changes, and the rationale for the changes, were made to the attached protocol in this amendment.

Section number and title in Protocol (28 Sep 2016)	**Section number and title in Amendment 1 (05 Oct 2016)**	**Original text:**	**Changed to:**	**Rationale:**
Title Page	Title Page	Date of Original Protocol: 28 September 2016	Date of Original Protocol: 28 September 2016 **Date of Amendment 1:** **5 October 2016**	Added the date of Amendment 1 to the Title Page.
Protocol Signature Page	Protocol Signature Page	Date of Original Protocol: 22 September 2016	**Date of Amendment 1:** **5 October 2016**	Revised the date of the signature page to be the date of Amendment 1.
Section 2, Synopsis, Endpoints	Section 2, Synopsis, Endpoints	In addition, plasma concentrations of SAGE-217, SAGE-217 metabolites, and HPβCD will be measured, and PK parameters will be derived.	In addition, plasma concentrations of SAGE-217 **and possibly** SAGE-217 metabolites will be measured, and PK parameters will be derived.	Clarified that plasma might be assayed for concentrations of SAGE-217 metabolites and removed assay of HPβCD.

Section number and title in Protocol (28 Sep 2016)	**Section number and title in Amendment 1 (05 Oct 2016)**	**Original text:**	**Changed to:**	**Rationale:**
Section 2, Synopsis, Exploratory Endpoints	Section 2, Synopsis, Exploratory Endpoints	[redacted]	[redacted]	[redacted]
Section 2, Synopsis, Pharmacokinetics	Section 2, Synopsis, Pharmacokinetics	Plasma will be collected to assay for concentrations of SAGE-217, SAGE-217 metabolites, and HPβCD	Plasma will be collected to assay for concentrations of SAGE-217 **and possibly** SAGE-217 metabolites.	Clarified that plasma might be assayed for concentrations of SAGE-217 metabolites and removed assay of HPβCD.
Section 2, Synopsis, Schedule of Events, Table 2 (Part A)	Section 2, Synopsis, Schedule of Events, Table 2 (Part A)	[redacted]	[redacted]	[redacted]
Section 2, Synopsis, Schedule of Events, Table 3 (Part B)	Section 2, Synopsis, Schedule of Events, Table 3 (Part B)	Screening (Day -28 to Day -1)	Screening (**Day -14** to Day -1)	Corrected timing of screening to be from Day -14 (not Day -28).
Section 2, Synopsis, Schedule of Events, Table 3 (Part B)	Section 2, Synopsis, Schedule of Events, Table 3 (Part B)	[redacted]	[redacted]	[redacted]

Section number and title in Protocol (28 Sep 2016)	**Section number and title in Amendment 1 (05 Oct 2016)**	**Original text:**	**Changed to:**	**Rationale:**
Section 6.3.3, Exploratory Endpoints	Section 6.3.3, Exploratory Endpoints	[redacted]	[redacted]	[redacted]
Section 10.4, Table 5	Section 10.4, Table 5	Sucralose concentration (mg/mL): 0.029; Sucralose amount (mg/bottle): 3.569	Sucralose concentration (mg/mL): **0.025**; Sucralose amount (mg/bottle): **3.124**	Corrected the sucralose concentration and amount per bottle.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Section number and title in Protocol (28 Sep 2016)	Section number and title in Amendment 1 (05 Oct 2016)	Original text:	Changed to:	Rationale:
				
Section 12.3, Sample Analysis	Section 12.3, Sample Analysis	Bioanalysis of plasma samples for the determination of concentrations of SAGE-217, SAGE-217 metabolites, and HPβCD will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory.	Bioanalysis of plasma samples for the determination of concentrations of SAGE-217 **and possibly** SAGE-217 metabolites will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory.	Clarified that plasma might be assayed for concentrations of SAGE-217 metabolites and removed assay of HPβCD.

Section number and title in Protocol (28 Sep 2016)	**Section number and title in Amendment 1 (05 Oct 2016)**	**Original text:**	**Changed to:**	**Rationale:**
Section 20, List of References	Section 20, List of References	Pritchett DB, Sontheimer H, Shivers BD, et al. Importance of a novel GABAA receptor subunit for benzodiazepine pharmacology. Nature. 1989;338(6216):582-5.	Deleted Pritchett et al., 1989	This reference was not cited within the text and was removed.
Appendix 9	Appendix 9	Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline, Version 1/14/09	Columbia-Suicide Severity Rating Scale (C-SSRS) **Baseline/Screening Version** 1/14/09	Replaced the Baseline version of the C-SSRS with the Baseline/Screening version of the C-SSRS.

Summary of Changes Page
Protocol 217-PRK-201
Date 05 Oct 2016

The following changes, and the rationale for the changes, were made to the attached protocol in this amendment.

Section number and title in Protocol (28 Sep 2016)	**Section number and title in Amendment 1 (05 Oct 2016)**	**Original text:**	**Changed to:**	**Rationale:**
Title Page	Title Page	Date of Original Protocol: 28 September 2016	Date of Original Protocol: 28 September 2016 **Date of Amendment 1:** **5 October 2016**	Added the date of Amendment 1 to the Title Page.
Protocol Signature Page	Protocol Signature Page	Date of Original Protocol: 22 September 2016	**Date of Amendment 1:** **5 October 2016**	Revised the date of the signature page to be the date of Amendment 1.
Section 2, Synopsis, Endpoints	Section 2, Synopsis, Endpoints	In addition, plasma concentrations of SAGE-217, SAGE-217 metabolites, and HPβCD will be measured, and PK parameters will be derived.	In addition, plasma concentrations of SAGE-217 **and possibly** SAGE-217 metabolites will be measured, and PK parameters will be derived.	Clarified that plasma might be assayed for concentrations of SAGE-217 metabolites and removed assay of HPβCD.

Section number and title in Protocol (28 Sep 2016)	**Section number and title in Amendment 1 (05 Oct 2016)**	**Original text:**	**Changed to:**	**Rationale:**
Section 2, Synopsis, Exploratory Endpoints	Section 2, Synopsis, Exploratory Endpoints	[redacted]	[redacted]	[redacted]
Section 2, Synopsis, Pharmacokinetics	Section 2, Synopsis, Pharmacokinetics	Plasma will be collected to assay for concentrations of SAGE-217, SAGE-217 metabolites, and HPβCD	Plasma will be collected to assay for concentrations of SAGE-217 **and possibly** SAGE-217 metabolites.	Clarified that plasma might be assayed for concentrations of SAGE-217 metabolites and removed assay of HPβCD.
Section 2, Synopsis, Schedule of Events, Table 2 (Part A)	Section 2, Synopsis, Schedule of Events, Table 2 (Part A)	[redacted]	[redacted]	[redacted]
Section 2, Synopsis, Schedule of Events, Table 3 (Part B)	Section 2, Synopsis, Schedule of Events, Table 3 (Part B)	Screening (Day -28 to Day -1)	Screening (**Day -14** to Day -1)	Corrected timing of screening to be from Day -14 (not Day -28)
Section 2, Synopsis, Schedule of Events, Table 3 (Part B)	Section 2, Synopsis, Schedule of Events, Table 3 (Part B)	[redacted]	[redacted]	[redacted]

Section number and title in Protocol (28 Sep 2016)	**Section number and title in Amendment 1 (05 Oct 2016)**	**Original text:**	**Changed to:**	**Rationale:**
Section 6.3.3, Exploratory Endpoints	Section 6.3.3, Exploratory Endpoints	[redacted]	[redacted]	[redacted]
Section 10.4, Table 5	Section 10.4, Table 5	Sucralose concentration (mg/mL): 0.029; Sucralose amount (mg/bottle): 3.569	Sucralose concentration (mg/mL): **0.025**; Sucralose amount (mg/bottle): **3.124**	Corrected the sucralose concentration and amount per bottle.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Section number and title in Protocol (28 Sep 2016)	**Section number and title in Amendment 1 (05 Oct 2016)**	**Original text:**	**Changed to:**	**Rationale:**
				
Section 12.3, Sample Analysis	Section 12.3, Sample Analysis	Bioanalysis of plasma samples for the determination of concentrations of SAGE-217, SAGE-217 metabolites, and HPβCD will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory.	Bioanalysis of plasma samples for the determination of concentrations of SAGE-217 **and possibly** SAGE-217 metabolites will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory.	Clarified that plasma might be assayed for concentrations of SAGE-217 metabolites and removed assay of HPβCD.

Section number and title in Protocol (28 Sep 2016)	**Section number and title in Amendment 1 (05 Oct 2016)**	**Original text:**	**Changed to:**	**Rationale:**
Section 20, List of References	Section 20, List of References	Pritchett DB, Sontheimer H, Shivers BD, et al. Importance of a novel GABAA receptor subunit for benzodiazepine pharmacology. Nature. 1989;338(6216):582-5.	Deleted Pritchett et al., 1989	This reference was not cited within the text and was removed.
Appendix 9	Appendix 9	Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline, Version 1/14/09	Columbia-Suicide Severity Rating Scale (C-SSRS) **Baseline/Screening Version** 1/14/09	Replaced the Baseline version of the C-SSRS with the Baseline/Screening version of the C-SSRS.

1. TITLE PAGE

PROTOCOL NUMBER: 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

IND NUMBER: 131,258

Investigational Product	SAGE-217
Clinical Phase	2
Sponsor	Sage Therapeutics, Inc.
Sponsor Contact	[redacted], M.D., Ph.D. [redacted] Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: [redacted] Email: [redacted]
Medical Monitor	_ , M.D., M.P.H. Study Physician Sage Therapeutics 215 First Street Cambridge, MA 02142 Phone: [redacted] Email: [redacted]
Date of Odginal Protocol	28 September 2016

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

PROTOCOLSIGNATURE PAGE

Pro tocol Number: 217-PRK-201
Product: SAGE-217 Oral Solution
IND No.: 131,258
Study Ph;ise: 2
Sponsor: Sage Therapeutics
Date of Origim1l Pr otocol: Version 1.0 22 September 2016

Sponsor Approval

[redacted]
M.D [redacted]h.D.
28 Sep 2016
Date (DD/MMM/YYYY)

[redacted]
Pharm [redacted] M.S., R.Ph.
28 Sept 2016
Date (DD/MMM/YYYY)

[redacted]
Therapeutics
[redacted]
[redacted] M.S.H.S.
[redacted]
29 Sep 2016
Date (DD/MMM/YYYY)

[redacted]
[redacted] M.S.
Statist ician
Sage Therapeutics
28 SEP 2016
Date (DD/MMM/YYYY)

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the Clinical Protocol 217-PRK-201 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

CONTACTS IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Research Organization	[redacted]	[redacted]

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics
215 First Street
Cambridge, MA 02142

Name of Investigational Product:
SAGE-217 Oral Solution

Name of Active Ingredient:
SAGE-217

Title of Study: 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 (PD) of Moderate Severity Responding to Immediate-Release Levodopa/Carbidopa and Withdrawn from Levodopa/Carbidopa

Study centers: Up to 4 centers

Objectives:

Primary:

- To evaluate the safety and tolerability of SAGE-217 Oral Solution.

Secondary:

- 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.
- To compare the effect of SAGE-217 Oral Solution in combination with immediate-release oral Levodopa/Carbidopa to Levodopa/Carbidopa alone.

Endpoints:

Primary:

- Frequency and severity of adverse events and changes 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.

Secondary:

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) score.

Part B:

- Improvementin PD motor symptoms as assessed by changes in the MDS-UPDRS - Pait III score.
- Improvement in PD overall symptoms as assessed by changes in the MDS-UPDRS - Patts I-IV total score.
- Sleepiness/sedation as assessed by the Stanford SleepinessScale (SSS) and Modified Obse1ver's Assessment of Analgesia/Sedation(MOAAIS) scores.

In addition, plasma concentrations of SAGE-217, SAGE-217 metabolites, and hydroxypropyl-beta-cyclodextiin (HPPCD) will be measured, and PK pai·amteers will be derived.

Exploratory Endpoints:

[redacted]

Methodology:

This study will assess the safety, tolerability, pha1macokinetics (PK), and efficacy of SAGE-217 Oral Solution. For ease of discussion, Levodopa alone or Cai·bidopa-Levodopacombination will be refened to as Levodopa in this protocol.

There ai·e two pa1t:s

Part A: Open-label with morning (AM) dosing (4 days).

All subjects will continue to take their antipai·lcinso nian agents includingimmediate-releaseoral Levodopa on the day of admission(Day -1) and in the AM the following 3 days (Days 1 to 3). All subjects will stop their immediate-release oral Levodopa on Day 4 and will strut on a 30 mg dose of SAGE-217 Oral Solution administered in the AM with food. Subjects not tolerating 30 mg will receive 20 mg, and subjects not tolerating 20 mg will receive 10 mg on subsequent days. The dose received on Day 7 will be defined as the toleratteddose for that subject. Subjects not tolerating 10 mg will not be able to continue in the study and may be replaced. Subjects will be followedfor an additional 7 days (Day 14) after the administration of the last dose. Levodopatreatment will be resumed on Day 8 and continue through Day 14.

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

Pait A is designed to dete1mine the tolerated dose of SAGE-217 Oral Solution for each subject and to assess whether SAGE-217 exhibits efficacy in subjects with PD in order to info1m the conduct of Pait B.

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

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. Subjects randomized to the combination arm of Levodopa and SAGE-217 Oral Solution will receive this combination in the morning for the first 4 days (Days 1 to 4). Subjects randomized to the Levodopa plus placebo arm will receive Levodopa and SAGE-217 matching placebo oral solution 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).

All doses of SAGE-217 Oral Solution (or placebo) will be administered in the morning with food. If subjects are taking Levodopa as opposed to Carbidopa-Levodopa, administration with or without food will be determined by the Investigator.

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 adverse event 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 defined as 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 (Table 2 and Table 3, respectively).

Number of patients (planned):

Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14 to inform the conduct of Part B. Twelve subjects are anticipated to be randomized in Part B.

Diagnosis and main criteria for inclusion: All of the following inclusion and exclusion criteria will be applied during screening for Part A, with some of the criteria applied during screening for Part B, as indicated.

Inclusion criteria:

1. Subject has signed an informed consent form (ICF) before any study-specific procedures are performed.
2. Subject is between 40 and 75 years of age, inclusive.
3. Subject has a diagnosis of idiopathic PD based on modified UK Brain Bank Criteria (modified to allow individuals with a family history of PD) (Hughes 1992; Appendix 1).
4. Subjects with PD with a duration of less than 7 years and must meet the criteria for Hoehn and Yahr stage 2 or stage 3 (Appendix 2).
5. Subject has a stable dose of antiparkinsonian agents including immediate-release oral Levodopa or Carbidopa-Levodopa (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.

6. Subject is willing to discontinue his/her treatment with immediate-release oral Levodopa or Carbidopa-Levodopa for at least 8 hours prior to dosing with SAGE-217. (Part B also)
7. Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) or amantadine at least 5 days prior to the day of admission (Day -1). (Part B also)
8. Subjects taking an antidepressant drug, sleep medication, or neuroleptic must have been on a stable dose for at least 1 month prior to the baseline visit.
9. Subjects must have a MoCA score of >22.
10. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests. (Part B also)
11. Female subjects must agree to practice a highly effective method of birth control while on study, and for 30 days after receiving the last dose of study drug. Highly effective methods of birth control include combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence. (Part B also)
12. Male subjects must agree to practice a highly effective method of birth control while on study, and for 13 weeks after receiving the last dose of study drug. Effective methods of birth control include sexual abstinence, vasectomy, or a condom with spermicide (men) in combination with female partner's highly effective method. (Part B also)
13. Males must be willing to abstain from sperm donation and females from donating eggs while on study through 13 weeks after receiving the last dose of study drug. (Part B also)

Exclusion criteria:

1. Subjects with a known hypersensitivity to SAGE-217 Oral Solution or its major excipient, HPβCD. (Part B also)
2. Subjects with early PD (Hoehn and Yahr stage 1) or advanced PD (Hoehn and Yahr stage 4 or stage 5).
3. Subjects with any medical or psychiatric condition that jeopardizes/compromises his/her ability for participation. This includes schizophrenia spectrum and other psychotic disorders, substance-related and addictive disorders, feeding and eating disorders, bipolar and related disorders, structural brain disease including but not limited to history of encephalitis or hydrocephalus and history of clinically significant stroke, or anticipating starting psychotherapy or behavior therapy during the course of the study or who started psychotherapy or behavior therapy within 30 days prior to Part A Day 1.
4. Subjects with a history of:
   a. Electroconvulsive therapy;
   b. Stereotaxic brain surgery (deep brain stimulation) for PD;
   c. History of suicide attempt within 2 years, or has answered YES to questions 3, 4, or 5 on the C SSRS at the screening or Day -1 visits, or has current suicidal ideation; or
   d. Impulse control disorder.
5. Subjects with severe depression as defined by a BDI-II score >19.
6. Subjects with Type I or Type II diabetes mellitus.
7. Subjects with presence of drug-induced parkinsonism (eg, metoclopramide, flunarizine), metabolic identified neurogenetic disorders (eg, Wilson's disease), encephalitis, or other atypical Parkinsonian syndromes (eg, progressive supranuclear palsy, multiple system atrophy). (Part B also)
8. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.

(Part B also)

9. Subject has clinically significant abnormal physical examination OR 12-lead ECG at the screening or admission visits. NOTE: QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study. ECG may be repeated once if initial values obtained are outside the specified limits. (Part B also)
10. Subject has a history, presence and/or current evidence of serologic positive results for hepatitis B surface antigen (HbsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies 1 and 2.
11. Subject has exposure to another investigational medication or device within 30 days prior to Part A Day 1.
12. Subject has donated one or more units of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing (1 unit = 450 mL). (Part B also)
13. Subject is unwilling or unable to comply with study procedures. (Part B also)
14. Subjects has used any known strong inhibitors and/or inducers of cytochrome P450 (CYP)3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug. (Part B also)

Investigational product, dosage and mode of administration:

SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dose.

Duration of treatment: 7 days in Part A; 8 days in Part B

Part A:

Screening duration: up to 28 days; Treatment Period: 7 days; Follow-up: 7 days

Planned participation per subject: approximately 42 days during Part A.

Part B:

Screening duration: up to 14 days; Treatment Period: 8 days; Follow-up: 14 days

Planned participation per subject: approximately 36 days during Part B.

Reference therapy, dosage and mode of administration:

In part B, placebo will be matched to SAGE-217 Oral Solution.

Criteria for evaluation:

Safety and tolerability:

Safety and tolerability of study drug will be evaluated by vital signs, clinical laboratory measures, ECGs, physical examinations, concomitant medication usage, C-SSRS, and adverse event reporting. Sleepiness/sedation will be assessed by the SSS and MOAA/S.

Efficacy:

Improvement in PD motor symptoms and overall symptoms will be assessed by changes in the MDS-UPDRS Part III score and MDS-UPDRS Parts I-IV total score at various time points.

Pharmacokinetics:

Plasma will be collected to assay for concentrations of SAGE-217, SAGE-217 metabolites, and HPβCD. The following PK parameters will be derived from the plasma concentrations (where evaluable): area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), the distributional half-life and terminal half-life ($t_{1/2}$), and steady-state drug concentration in the plasma (C_{ss}).

Statistical methods:

Study Populations

The safety population, defined as all subjects who are administered study drug, will be used to provide descriptive summaries of safety.

The efficacy population, defined as all subjects in the safety population who receive at least one dose of study drug and have at least one postdose MDS-UPDRS evaluation, will be used to analyze efficacy data.

The PK population will consist of all subjects in the safety population with sufficient plasma concentrations for PK evaluations and will be used to summarize PK data.

Separate populations will be defined for each part of the study.

General Considerations

Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and summarized descriptively. For categorical endpoints, descriptive summaries will include counts and percentages.

Safety Analysis

Adverse events will be coded using Medical Dictionary for Regulatory Activities™ (MedDRA). The overall incidence of adverse events will be displayed by System Organ Class (SOC), preferred term, dose group, and cohort. Incidence of adverse events will also be presented by maximum severity and relationship to study drug. Vital signs, clinical laboratory measures, ECG, and C-SSRS data will be summarized by dose group and cohort, where applicable. Out-of-range safety endpoints may be categorized as low or high, where applicable.

Efficacy Analysis

Efficacy data will be summarized using appropriate descriptive statistics and other data presentation methods where applicable; subject listings will be provided for all efficacy data.

An interim analysis of 10 subjects completing Part A is planned to inform Part B study conduct.

Pharmacokinetic Analysis

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics and listed by subject.

Table 2: Schedule of Events: Part A (Open-Label)

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	X	X			X		X
MDS-UPDRS (Part III only)[k]							X	X		X	

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)
[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]; [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 Admission (Day -1); predose for Day 4, Day 6, and Day 8; and Day 14

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

[d] Vital Signs: Screening and 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. 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.

[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 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), predose Day 1, Day 2, Day 3, and Day 4; postdose on Day 7; 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 5, 6, and 8.

[p] Plasma PK sampling times (±5 minutes): Day 4 predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose; predose 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

Table 3: Schedule of Events: Part B (Randomized, Placebo-Controlled)

Visit Days	Screening (Day -28 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		X	X
MDS-UPDRS (Part III only)[k]				X	X		X	X	X		X		
[redacted]													

Visit Days	Screening (Day -28 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
[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), predose on Day 1 and Day 4; postdose on Day 8; and Days 15 and 22.

[k] MDS-UPDRS (Part III only): 2 (±10 minutes), 4 (±10 minutes), 8 (±15 minutes), and 12 (±15 minutes) hours postdose on Days 2, 3, 5, 6, 7, and 9.

[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.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

1. TITLE PAGE 1
2. SYNOPSIS 6
3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES 18
4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 25
5. INTRODUCTION 27
5.1. Background of Parkinson's Disease and Unmet Medical Need 27
5.2. SAGE-217 Oral Solution 28
5.3. Summary of Nonclinical and Clinical Experience with SAGE-217 28
5.3.1. Nonclinical Studies with SAGE-217 28
5.3.2. Clinical Experience 28
5.4. Potential Risks and Benefits 30
6. TRIAL OBJECTIVES AND PURPOSE 31
6.1. Primary Objective 31
6.2. Secondary Objectives 31
6.3. Endpoints 31
6.3.1. Primary Endpoints 31
6.3.2. Secondary Endpoints 31
6.3.3. Exploratory Endpoints 31
7. INVESTIGATIONAL PLAN 33
7.1. Overall Study Design 33
7.2. Number of Subjects 34
7.3. Treatment Assignment 34
7.4. Dose Adjustment Criteria 35
7.5. Criteria for Study Termination 35
8. SELECTION AND WITHDRAWAL OF SUBJECTS 37
8.1. Subject Inclusion Criteria 37
8.2. Subject Exclusion Criteria 38
8.3. Entrance Criteria for Part B 39
8.4. Subject Withdrawal Criteria 39

9. TREATMENT OF SUBJECTS 40
9.1. Description of Study Drug 40
9.1.1. Part A 40
9.1.2. Part B 40
9.2. Concomitant Medications 40
9.2.1. Prior/Concomitant Medications 40
9.2.2. Prohibited Medications 41
9.3. Treatment Compliance 41
9.4. Randomization and Blinding 41
10. STUDY DRUG MATERIALS AND MANAGEMENT 43
10.1. Study Drug 43
10.2. Study Drug Packaging and Labeling 43
10.3. Study Drug Storage 43
10.4. Study Drug Preparation 44
10.5. Administration 44
10.6. Study Drug Accountability 45
10.7. Study Drug Handling and Disposal 45
11. ASSESSMENT OF EFFICACY 46
11.1. Movement Disorder Society – Unified Parkinson's Disease Rating Scale 46
11.2. Exploratory Endpoints 47
[redacted] [redacted] 47
[redacted] [redacted] 47
[redacted] [redacted] 47
[redacted] [redacted] 48
[redacted] [redacted] 48
12. PHARMACOKINETICS 50
12.1. Blood Sample Collection 50
12.2. Storage and Shipment of Pharmacokinetic Samples 50
12.3. Sample Analysis 50
13. ASSESSMENT OF SAFETY 51
13.1. Safety and Tolerability Parameters 51
13.1.1. Demographic/Medical History 51
13.1.2. Vital Signs 51

13.1.3. Weight and Height 51
13.1.4. Physical Examination 51
13.1.5. Electrocardiogram (ECG) 51
13.1.6. Laboratory Assessments 52
13.1.6.1. Hematology 52
13.1.6.2. Blood Chemistry 52
13.1.6.3. Urinalysis 52
13.1.6.4. Virus Serology 52
13.1.6.5. Pregnancy Screen 53
13.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS) 53
13.1.8. Stanford Sleepiness Scale (SSS) 53
13.1.9. Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S) 53
13.2. Adverse and Serious Adverse Events 54
13.2.1. Definition of Adverse Events 54
13.2.1.1. Adverse Event 54
13.2.1.2. Suspected Adverse Reaction 54
13.2.1.3. Serious Adverse Event 54
13.2.1.4. Recording Sedation as an Adverse Event 55
13.2.2. Pregnancy 55
13.3. Relationship to Study Drug 55
13.4. Recording Adverse Events 56
13.5. Reporting Serious Adverse Events 56
14. STATISTICAL METHODS AND CONSIDERATIONS 58
14.1. Data Analysis Sets 58
14.2. Handling of Missing Data 58
14.3. Demographics and Baseline Characteristics 58
14.4. Efficacy Endpoints 58
14.4.1. Secondary Efficacy Endpoints 58
14.4.2. Exploratory Efficacy Endpoints 58
14.5. Safety and Tolerability Analyses 59
14.5.1. Adverse Events 59
14.5.2. Vital Signs 59
14.5.3. Physical Examinations 59

14.5.4. 12-Lead ECG 60
14.5.5. Clinical Laboratory Evaluations 60
14.5.6. Columbia-Suicide Severity Rating Scale (C-SSRS) 60
14.5.7. Stanford Sleepiness Scale (SSS) 60
14.5.8. Modified Observer's Assessment of Alertness/Sedation (MOAA/S) 60
14.5.9. Prior and Concomitant Medications 60
14.6. Pharmacokinetic Analysis 61
14.7. Determination of Sample Size 61
14.8. Changes From Protocol Specified Analyses 61
15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS 62
15.1. Study Monitoring 62
15.2. Audits and Inspections 62
15.3. Institutional Review Board (IRB) 63
16. QUALITY CONTROL AND QUALITY ASSURANCE 64
17. ETHICS 65
17.1. Ethics Review 65
17.2. Ethical Conduct of the Study 65
17.3. Written Informed Consent 65
18. DATA HANDLING AND RECORDKEEPING 66
18.1. Inspection of Records 66
18.2. Retention of Records 66
18.3. Confidentiality 66
19. PUBLICATION POLICY 68
20. LIST OF REFERENCES 69
21. APPENDICES 71
APPENDIX 1. UNITED KINGDOM BRAIN BANK CRITERIA 72
APPENDIX 2. HOEHN AND YAHR STAGING CRITERIA 73
APPENDIX 3. ANTICHOLINERGIC DRUGS 74
APPENDIX 4. MOVEMENT DISORDER SOCIETY-UNIFIED PARKINSON'S DISEASE RATING SCALE (MDS-UPDRS) 75
[redacted] 76
[redacted] 77
[redacted] 80

[redacted] 81
APPENDIX 9. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION AND SINCE LAST VISIT VERSION 84
APPENDIX 10. STANFORD SLEEPINESS SCALE (SSS)..... 90
APPENDIX 11. MODIFIED OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (MOAA/S)..... 91

LIST OF TABLES

Table 1: Emergency Contact Information 5
Table 2: Schedule of Events: Part A (Open-Label) 12
Table 3: Schedule of Events: Part B (Randomized, Placebo-Controlled) 15
Table 4: Abbreviations and Specialist Terms 25
Table 5: Batch Formula for 125 mL of Stock SAGE-217 Oral Solution 6 mg/mL 44
Table 6: Rating Scale for the MDS-UPDRS 46

LIST OF FIGURES

Figure 1: Study Design of Part A 36
Figure 2: Study Design of Part B 36

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 4: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ALT	alanine aminotransferase
AM	morning
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
[redacted]	[redacted]
BMI	body mass index
CBC	complete blood count
C_{max}	maximum plasma concentration
CRF	case report form
CS	clinically significant
Css	steady-state drug concentration in the plasma
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic CRF
EP	European Pharmacopeia
GABA	γ aminobutyric acid
$GABA_A$	γ aminobutyric acid-ligand gated chloride channel
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPβCD	hydroxypropyl-β-cyclodextrin
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board

Abbreviation or Specialist Term	Explanation
Levodopa/Carbidopa	Levodopa or Carbidopa-Levodopa
MDS	Movement Disorder Society
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
MoCA	Montreal Cognitive Assessment
MTD	maximum tolerated dose
n	number
NCS	not clinically significant
NF	National Formulary
PD	Parkinson's disease
[redacted]	[redacted]
PK	pharmacokinetic(s)
PM	evening
QTcF	QT interval calculated using the Fridericia method
SOC	system organ class
SRC	Safety Review Committee
SSS	Stanford Sleepiness Scale
TEAE	treatment-emergent adverse event
$t_{1/2}$	terminal half-life
t_{max}	time to reach maximum concentration
USP	United States Pharmacopeia
WHO	World Health Organization

5. INTRODUCTION

5.1. Background of Parkinson's Disease and Unmet Medical Need

Parkinson's disease (PD) is a chronic progressive neurodegenerative condition that affects the motor, autonomic, cognitive, and sensory systems. Parkinson's disease is the second most common neurodegenerative disorder (Bergman 2002) and is associated with a massive loss of dopaminergic cells in the substantia nigra, leading to dopamine hypofunction and alteration of the basal ganglia circuitry. Dopamine neurons are under the control of the excitatory glutamatergic and inhibitory γ-aminobutyric acid (GABA) systems. Imbalance between the glutamatergic and GABA systems may contribute to excitotoxicity and dopaminergic cell death.

The motor symptoms of PD have been linked with a loss of dopamine neurons in the substantia nigra pars compacta and a consequential reduction in the level of dopamine input in the striatum (Siderowf 2012). These symptoms evolve slowly and are characterized by the progression of tremor, rigidity, bradykinesia, and postural instability. Tremor caused by PD can appear as either a resting tremor or an action tremor. The most typical tremor of PD is a "pill-rolling" rest tremor between the thumb and index finger. Not everyone with PD develops a tremor, and those who do experience tremor may have symptoms that come and go. Typically, PD tremor starts in the fingers of one hand before spreading to affect the rest of the arm. Tremor can also spread to affect the foot on the same side of the body and, after several years, the tremor can spread to affect the other side of the body. Without treatment, PD tremor usually worsens over time.

At present, there is no cure for PD. The core symptoms are caused by the degeneration of dopamine-producing neurons and, therefore, treatment consists of dopamine replacement. While enormous progress has been made in the treatment of PD over the past half century, levodopa remains the most potent drug for controlling PD symptoms (Jankovic 2008). The addition of carbidopa, a peripheral dopa decarboxylase inhibitor, enhances the therapeutic benefits of levodopa. However, levodopa therapy is frequently associated with motor complications, and the appropriate time to initiate levodopa therapy continues to be debated (Stern 2004; Weiner 2004). The majority of patients treated with levodopa experience motor fluctuation, dyskinesia or other complications after 5 years of treatment (Jankovic 2005).

Neurosteroids, a group of steroid hormones synthesized in the brain, modulate the function of several neurotransmitter systems. The substantia nigra expresses high concentrations of allopregnanolone, a neurosteroid that positively modulates the action of GABA at γ-aminobutyric acid-ligand gated chloride channel ($GABA_A$) receptors. In PD patients, decreased plasma and cerebrospinal fluid levels of the neurosteroid allopregnanolone and 5α-dihydroprogesterone have been observed (di Michele 2003).

Parkinson's disease is the second most common chronic neurodegenerative disease, affecting about 1 million people in the United States and more than 4 million people worldwide. It has a devastating effect on patients and is often accompanied by tremendous physical and emotional burden not only for the patients but also for their families and friends. As the size of the elderly population grows, the burden of PD is projected to grow substantially over the next few decades. To date, the therapy of PD is symptomatic, aimed at ameliorating motor symptoms. Although the goal of therapy is to reverse the functional disability, abolition of all symptoms and signs is

not currently possible, even with high doses of medication. Thus, there is a growing need for innovative new treatments to prevent, delay onset, or alleviate symptoms of PD. Neurosteroids act as neuroprotectants and as $GABA_A$-receptor agonists in the physiology and pathology of the basal ganglia, impact dopaminergic cell activity and survival, and may therefore represent potential therapeutics in PD.

5.2. SAGE-217 Oral Solution

SAGE-217 is a positive allosteric modulator of the $GABA_A$ receptor and thus is expected to be of benefit for the treatment of PD.

SAGE-217 Oral Solution 6 mg/mL (40% w/w aqueous hydroxypropyl-β-cyclodextrin [HPβCD] with 0.025 mg/mL sucralose) is a non-viscous, clear solution.

5.3. Summary of Nonclinical and Clinical Experience with SAGE-217

5.3.1. Nonclinical Studies with SAGE-217

In nonclinical studies of SAGE-217, sedative-hypnotic effects were consistently observed at higher doses in both in vivo pharmacology studies and in toxicology studies. The sedative-hypnotic impairments seen with SAGE-217 were typical for $GABA_A$-positive modulators, ranging from hyperexcitability and ataxia at the lower doses through deep sedation and ultimately anesthesia at higher doses. Depth and duration of sedation demonstrated a clear dose response over the range tested, with evidence of tolerance occurring with continued exposure. Tolerance to the effects of SAGE-217 on motor incoordination was not observed after 7 days of dosing.

The compound has been assessed in 14-day rat and dog toxicology studies with daily administration of SAGE-217 as a solution in HPβCD in dogs and Labrasol® in rats. The no observed adverse effect level was 3 mg/kg (females) and 22.5 mg/kg (males) in rats and 2.5 mg/kg in dogs. There were no adverse effects in dogs or rats in the main toxicology studies. A single observation of mortality occurred in one female rat at the high dose in a toxicokinetic study that was suspected to have been related to exaggerated pharmacology. Additional toxicology and pharmacology information is provided in the Investigator's Brochure.

5.3.2. Clinical Experience

To date, two clinical studies employing SAGE-217 Oral Solution are clinically complete and final clinical study reports are pending. Discussions of pharmacokinetic (PK) data are limited to the single-ascending dose, food effect, and essential tremor cohorts from Study 217-CLP-101 and the multiple-ascending dose and drug-drug interaction cohorts from Study 217-CLP-102. Discussions of safety data are limited to the single-ascending dose cohorts in Study 217 CLP 101 and the multiple-ascending dose cohorts in Study 217-CLP-102.

Study 217-CLP-101 was a first-in-human, four-part study that assessed the effects of a single dose of SAGE-217. The study was a double-blind, placebo-controlled, single-ascending dose design in healthy adult volunteers, with the objective of identifying the maximum tolerated dose (MTD) and PK profiles of SAGE-217 Oral Solution. Subjects in each of the single-ascending dose cohorts received a single dose of study drug, either SAGE-217 (six subjects) or placebo (two subjects), with SAGE-217 doses of 0.25 mg, 0.75 mg, 2 mg, 5.5 mg, 11 mg, 22 mg, 44 mg,

55 mg, and 66 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the Safety Review Committee (SRC) and agreement reached that it was safe to increase the dose. The MTD was determined to be 55 mg. Two cohorts, 6 subjects each, received SAGE-217 Oral Solution in an open-label manner (one cohort received 50% of the MTD [22 mg] to study the food effects and the other cohort received the MTD [55 mg] to study the effects on subjects with essential tremor). SAGE-217 Oral Solution was orally bioavailable, demonstrated dose-linear PK from the lowest (0.25 mg) through the highest (66 mg) dose, and supported once-daily oral dosing with food. In addition, the pharmacodynamic effects of the SAGE-217 Oral Solution MTD were assessed in placebo-controlled, blinded, crossover electroencephalogram cohorts of 8 subjects each; one cohort received 50% of the MTD (22 mg) and the other received the MTD (55 mg).

Study 217-CLP-102 was a two-part study that assessed the effects of multiple-ascending doses of SAGE-217 Oral Solution. The study was a double-blind, placebo-controlled, multiple-ascending dose study in healthy adult volunteers. Subjects in each of the multiple-ascending dose cohorts received study drug, either SAGE-217 (nine subjects) or placebo (three subjects), once daily for 7 days, with SAGE-217 Oral Solution doses of 15 mg, 30 mg, and 35 mg. Escalation to the next dose was undertaken only after safety and PK data were reviewed by the SRC and agreement reached that it was safe to increase the dose. The MTD was determined to be 30 mg. It was observed that subjects receiving the drug in the evening did better in terms of tolerability compared to when they received the drug in the morning. A fourth cohort of 12 subjects received 30 mg of SAGE-217 Oral Solution in an open-label manner to study drug-drug interactions. SAGE-217 Oral Solution is not likely to induce the metabolism of cytochrome P450 (CYP)2B6 or CYP3A4 substrates. SAGE-217 Oral Solution was orally bioavailable and suitable for once-daily oral dosing at night time with food.

SAGE-217 Oral Solution was generally well tolerated. In both Phase 1 studies (217-CLP-101 and 217-CLP-102), doses were escalated until the stopping criteria were met. Most adverse events were reported as mild or moderate in intensity, and there were no serious adverse events reported in either study. In addition, none of the observed adverse events resulted in discontinuation of the study drug. At doses planned for further study, the observed sedation was mild, transient, and associated with daily peak exposure. The most common treatment-emergent adverse events (TEAEs) were sedation, somnolence, dizziness, euphoric mood, fatigue, tremor, and muscle twitching, reported most frequently in the highest dose group (66 mg). Some changes in mean blood pressure and heart rate were observed after single doses of 44 mg and greater. After multiple doses of 30 mg (morning [AM] or evening [PM]) or 35 mg (AM) over 7 days, there was no evidence of changes in mean vital sign measures even though Day 7 plasma concentrations approximated that of the highest single dose in the single-ascending dose study. Subjects seemed to tolerate SAGE-217 better when given as night time dosing.

Neuroactive steroids are a class of endogenous and synthetic positive allosteric modulators that target both synaptic and extra-synaptic $GABA_A$ receptors (Belelli 2002 and confirmed in the Sponsor's in vitro studies). This diverse activity profile suggests that neuroactive steroid $GABA_A$ receptor-positive allosteric modulators could exhibit robust activity against essential tremor. Administration of SAGE-547 injection, a proprietary formulation of the endogenous neuroactive steroid, resulted in significant reductions in upper limb kinetic tremor scores compared to placebo in a Phase 2 proof-of-principle study (IND 122,280). Based on these

results with SAGE-547, the study design for single-ascending dose study 217-CLP-101 included a cohort of subjects with essential tremor (N=6) who received SAGE-217 Oral Solution (55 mg) in an open-label manner. Data from this cohort indicate that single doses of SAGE-217 Oral Solution resulted in a reduction in the tremor symptoms, suggesting that SAGE-217 might be effective in treating PD.

There are no clinical efficacy data of SAGE-217 Oral Solution in PD, since the present study is the first study in this indication.

5.4. Potential Risks and Benefits

Protocol 217-PRK-201 is the first clinical study evaluating the efficacy of SAGE-217 Oral Solution in PD. Thus, the potential benefits in this population are unknown, although the risks are likely to be similar to those mentioned in the Investigator's Brochure. GABA compounds that cross the blood-brain barrier or increase GABA activity alleviate muscle stiffness caused by a lack of GABAergic tone (Winkler 1999), validating this receptor as a therapeutic target. Given the promising clinical data with another neuroactive steroid (SAGE-547) in conjunction with the shared broad receptor selectivity profile, oral bioavailability, long half-life, preclinical evidence of anxiolytic activity, and safety data of SAGE-217, it is possible that patients may have a clinical benefit at the exposures selected for this study. In view of the few risks associated with administration of SAGE-217 Oral Solution that have been identified to date, an intra-patient dose-reduction design has been chosen to permit reduction in dose based on tolerability (adverse events), specifically sedation, versus treatment effect. Each subject will start with an initial dose of 30 mg; subjects unable to tolerate 30 mg will receive 20 mg; subjects unable to tolerate 20 mg will receive 10 mg. The tolerated dose for each subject will be the dose taken on Day 7. Subjects who tolerate at least the 10 mg dose on Day 7 will be eligible to enroll in Part B. Given the high medical need and potential for benefit in PD, there is a favorable benefit-risk evaluation to investigate SAGE-217 Oral Solution in PD.

In conclusion, selection criteria for the proposed study take into account the potential safety risks. Continuous safety monitoring, and the implementation of a formal dose-reduction and study drug discontinuation scheme also have the potential to mitigate risk. From a benefit/risk perspective, the appropriate measures are being taken in order to ensure the safety of the subjects who will be enrolled.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of SAGE-217 Oral Solution.

6.2. Secondary Objectives

The secondary objectives of the study 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.
- To compare the effect of SAGE-217 Oral Solution in combination with immediate-release oral Levodopa/Carbidopa to Levodopa/Carbidopa alone.

6.3. Endpoints

6.3.1. Primary Endpoints

- Frequency and severity of adverse events and changes in vital signs, clinical laboratory data, electrncardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS) during both Part A and Pait B.

6.3.2. Secondary Endpoints

Part A:

- Improvement in PD motor symptoms as assessed by changes in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) - Pali III (Motor Examination) score.

Part B:

- Improvement in PD motor symptoms as assessed by changes in the MDS-UPDRS - Pait III score.
- Improvement in PD overall symptoms as assessed by changes in the MDS-UPDRS - Palis I-IV total score.
- Sleepiness/sedation as assessed by the Stanford Sleepiness Scale (SSS) and Modified Observer's Assessment of Analgesia/Sedation (MOAA/S) scores.

6.3.3. Exploratory Endpoints

I [redacted]

[redacted]

7. INVESTIGATIONAL PLAN

For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol.

7.1. Overall Study Design

This study is a two-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 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 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 morning with food, as outlined in Section 9.1.1. 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). 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 interim analysis.

  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 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. Subjects randomized to the Levodopa plus placebo arm will receive Levodopa and SAGE-217 matching 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 adverse event 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 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 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.

The study designs of Part A and Part B are displayed in Figure 1 and Figure 2, respectively. Assessments will be performed periodically during the study as outlined in the Schedule of Events for Part A and Part B (Table 2 and Table 3, respectively).

7.2. Number of Subjects

Approximately 18 subjects will be enrolled in Part A. An interim analysis is planned after 10 subjects have completed Part A through Day 14 to inform the conduct of Part B. Twelve subjects are anticipated to be randomized in Part B.

7.3. Treatment Assignment

SAGE-217 will be administered in the morning with food in Parts A and B. Food intake will be standardized as specified by the Sponsor. If subjects are taking Levodopa as opposed to Carbidopa-Levodopa, administration with or without food will be determined by the Investigator.

Part A of the study is open-label. Part B of the study is randomized, placebo-controlled, two-sequence crossover. Subjects will be randomly assigned in a 1:1 manner to receive open-label Levodopa plus blinded SAGE-217 Oral Solution or placebo for 4 days (Days 1 to 4, Period 1 of crossover). Subjects, clinicians, and the study team will be blinded to treatment allocation. The pharmacist, who will prepare the oral solutions according to the randomization schedule, will be

unblinded. For the remaining 4 days of Part B (Days 5 to 8, Period 2 of crossover), all subjects will discontinue Levodopa and will receive their individually established tolerated dose of SAGE-217 Oral Solution from Part A in an open-label manner.

Dose reductions for lack of tolerability will be allowed during both parts of the study (Section 7.4).

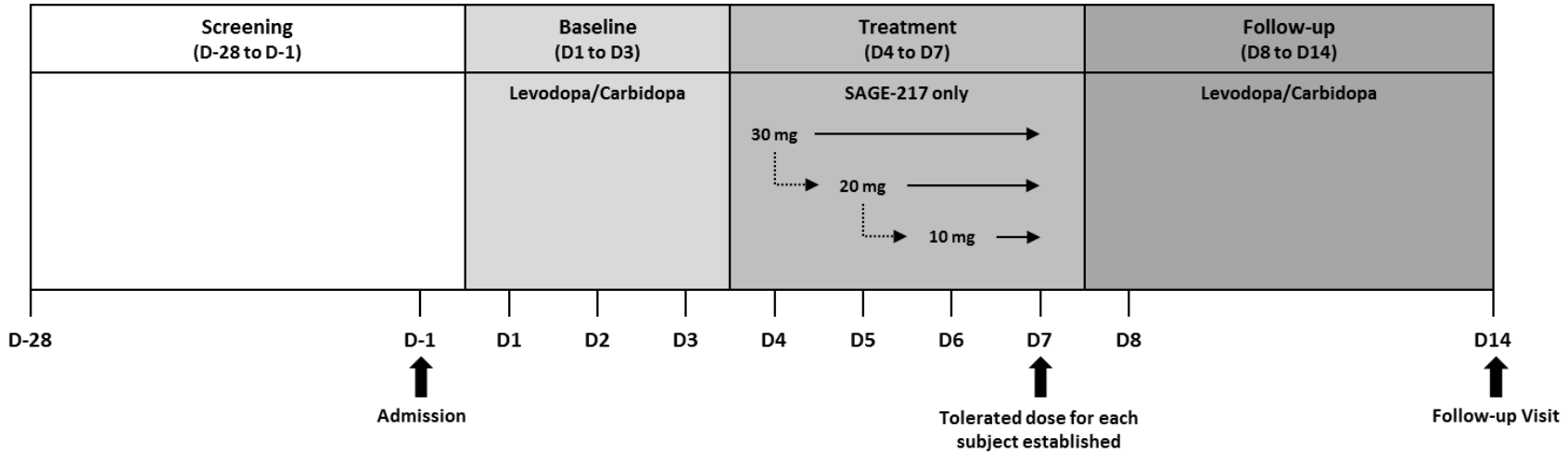
7.4. Dose Adjustment Criteria

Dose reductions of SAGE-217 for lack of tolerability will be allowed during both parts of the study. If at any time the dose is not tolerated in Part A, as determined by the Investigator, the dose on the next day will be reduced to the next lowest dose (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 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

7.5. Criteria for Study Termination

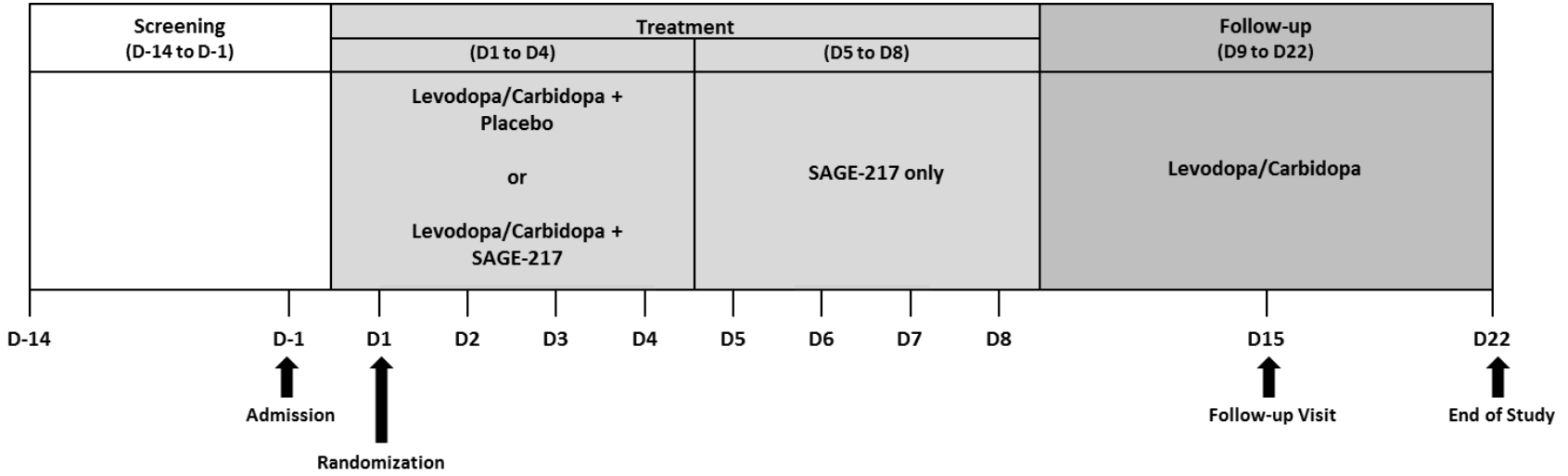
Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons, including the occurrence of adverse events or other findings suggesting unacceptable risk to subjects, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their Institutional Review Board (IRB) and initiate withdrawal procedures for participating subjects.

Figure 1: Study Design of Part A



NOTE: In order to qualify for Part B of the study, a subject must tolerate a dose of at least 10 mg of SAGE-217 Oral Solution in Part A.

Figure 2: Study Design of Part B



NOTE: Part B will be initiated only after review of the Part A interim analysis (after 10 subjects have completed Part A).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

It is anticipated that up to 18 subjects will be enrolled in Part A at up to 4 study centers. All of the following inclusion and exclusion criteria will be applied during screening for Part A, with some of the criteria applied during screening for Part B, as indicated.

8.1. Subject Inclusion Criteria

Subjects must meet the following inclusion criteria for enrollment in the study:

1. Subject has signed an informed consent form (ICF) before any study-specific procedures are performed.
2. Subject is between 40 and 75 years of age, inclusive.
3. Subject has a diagnosis of idiopathic PD based on modified UK Brain Bank Criteria (modified to allow individuals with a family history of PD) (Hughes 1992; Appendix 1).
4. Subjects with PD with a duration of less than 7 years and must meet the criteria for Hoehn and Yahr stage 2 or stage 3 (Appendix 2).
5. Subject has a stable dose of antiparkinsonian agents including immediate-release oral Levodopa or Carbidopa-Levodopa (defined as no changes for a period of at least 1 month prior to the baseline visit) and is expected to remain on this stable dose for the duration of this study.
6. Subject is willing to discontinue his/her treatment with immediate-release oral Levodopa or Carbidopa-Levodopa for at least 8 hours prior to dosing with SAGE-217. (Part B also)
7. Subject is willing to discontinue his/her treatment with anticholinergics (Appendix 3) or amantadine at least 5 days prior to the day of admission (Day -1). (Part B also)
8. Subjects taking an antidepressant drug, sleep medication, or neuroleptic must have been on a stable dose for at least 1 month prior to the baseline visit.
9. Subjects must have a MoCA score of >22.
10. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests. (Part B also)
11. Female subjects must agree to practice a highly effective method of birth control while on study, and for 30 days after receiving the last dose of study drug. Highly effective methods of birth control include combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, or sexual abstinence. (Part B also)
12. Male subjects must agree to practice a highly effective method of birth control while on study, and for 13 weeks after receiving the last dose of study drug. Effective methods of birth control include sexual abstinence, vasectomy, or a condom with spermicide (men) in combination with female partner's highly effective method. (Part B also)

13. Males must be willing to abstain from sperm donation and females from donating eggs while on study through 13 weeks after receiving the last dose of study drug. (Part B also)

8.2. Subject Exclusion Criteria

Subjects who met any of the following exclusion criteria will be excluded from the study:

1. Subjects with a known hypersensitivity to SAGE-217 Oral Solution or its major excipient, HPβCD. (Part B also)
2. Subjects with early PD (Hoehn and Yahr stage 1) or advanced PD (Hoehn and Yahr stage 4 or stage 5).
3. Subjects with any medical or psychiatric condition that jeopardizes/compromises his/her ability for participation. This includes schizophrenia spectrum and other psychotic disorders, substance-related and addictive disorders, feeding and eating disorders, bipolar and related disorders, structural brain disease including but not limited to history of encephalitis or hydrocephalus and history of clinically significant stroke, or anticipating starting psychotherapy or behavior therapy during the course of the study, or who started psychotherapy or behavior therapy within 30 days prior to Part A Day 1.
4. Subjects with a history of:
    a. Electroconvulsive therapy;
    b. Stereotaxic brain surgery (deep brain stimulation) for PD;
    c. History of suicide attempt within 2 years, or has answered YES to questions 3, 4, or 5 on the C-SSRS at the screening or Day -1 visits, or has current suicidal ideation; or
    d. Impulse control disorder.
5. Subjects with severe depression as defined by a BDI-II score >19.
6. Subjects with Type I or Type II diabetes mellitus.
7. Subjects with presence of drug-induced parkinsonism (eg, metoclopramide, flunarizine), metabolic identified neurogenetic disorders (eg, Wilson's disease), encephalitis, or other atypical Parkinsonian syndromes (eg, progressive supranuclear palsy, multiple system atrophy). (Part B also)
8. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease. (Part B also)
9. Subject has clinically significant abnormal physical examination OR 12-lead ECG at the screening or admission visits. NOTE: QT interval calculated using the Fridericia method (QTcF) of >450 msec in males or >470 msec in females will be the basis for exclusion from the study. ECG may be repeated once if initial values obtained are outside the specified limits. (Part B also)
10. Subject has a history, presence and/or current evidence of serologic positive results for hepatitis B surface antigen (HbsAg), hepatitis C (HCV) antibodies, or human immunodeficiency virus (HIV) antibodies 1 and 2.

11. Subject has exposure to another investigational medication or device within the prior 30 days.
12. Subject has donated one or more units of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing (1 unit = 450 mL). (Part B also)
13. Subject is unwilling or unable to comply with study procedures. (Part B also)
14. Subject has used any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug. (Part B also)

8.3. Entrance Criteria for Part B

In addition to the inclusion and exclusion criteria determined at screening for Part B indicated in Section 8.1 and Section 8.2, respectively, subjects must be able to tolerate at least 10 mg of SAGE-217 in Part A in order to be enrolled into Part B. Part B will not be initiated until results of the Part A interim analysis have been reviewed.

8.4. Subject Withdrawal Criteria

Participation in the study is strictly voluntary. Subjects are free to discontinue the study at any time without giving their reason(s).

A subject must be withdrawn from the study treatment in the event of any of the following:

- Withdrawal of the subject's consent;
- New onset of a condition that would have met exclusion criterion, is clinically relevant and affects the subject's safety, and discontinuation is considered necessary by the Investigators and/Sponsor;
- Occurrence of intolerable adverse events;
- Occurrence of pregnancy;
- Intake of nonpermitted concomitant medication;
- Subject noncompliance;
- Significant protocol deviation determined in consultation with the Medical Monitor.

If a subject fails to attend scheduled assessments during the course of the study, the Investigators must determine the reasons and the circumstances as completely and accurately as possible and document this in the subject's source documents.

Subjects may be withdrawn from the study if there is concern for the subject's safety or it is determined that the subject is no longer a qualified participant. Any subject who is withdrawn from the study for any reason is to have the final visit assessments performed.

Subjects who withdraw or are withdrawn from the study may be replaced.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

For ease of discussion, Levodopa alone or Carbidopa-Levodopa combination will be referred to as Levodopa in this protocol.

9.1.1. Part A

Subjects participating in Part A of the study will take study drug (SAGE-217) in an open-label manner. 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 the following 3 days (Days 1 to 3). On the morning of Day 4, subjects will stop their immediate-release oral Levodopa and take SAGE-217 for 4 days (Days 4 to 7) in the AM with food. On Day 4, subjects will receive a 30 mg dose of SAGE-217. Subjects not tolerating 30 mg will receive 20 mg the next day, and subjects not tolerating 20 mg will receive 10 mg the next day. The dose received on Day 7 will be defined as the tolerated dose for that subject, with this dose to be used as the starting dose for Part B for that subject.

Subjects not tolerating 10 mg will not be able to continue in the study and may be replaced. Levodopa treatment will be resumed on Day 8 and continue through Day 14.

9.1.2. Part B

In order to qualify for Part B of the study, a subject must tolerate a dose of at least 10 mg of SAGE-217 Oral Solution. On Day 1 of Part B, subjects will be randomized in a 1:1 manner to open-label Levodopa plus blinded SAGE-217 Oral Solution or placebo.

- Subjects randomized to the Levodopa plus placebo arm will receive Levodopa plus SAGE-217 matching placebo oral solution in the AM for the first 4 days (Days 1 to 4).
- Subjects randomized to the Levodopa plus SAGE-217 Oral Solution arm 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.

9.2. Concomitant Medications

9.2.1. Prior/Concomitant Medications

Any concomitant medication determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study under the guidance outlined in Section 9.2.

Record the name, start date (if known), indication for use and whether ongoing or stopped of medications/treatments taken within 2 weeks prior to study entry as well as any medications taken during the study.

The charts of all study participants will be reviewed for new concomitant medications through discharge from the unit. Chart reviews will include examination of nursing and physician progress notes, vital signs, and medication records in order to identify adverse events that may be associated with new concomitant medications. New concomitant medications, ongoing concomitant medications with a change in dose, and medical procedures ordered (eg, laboratory assessments, computed tomography or magnetic resonance imaging scans) will be reviewed to determine if they are associated with an adverse event not previously identified.

The Investigator will document all doses of Levodopa and Carbidopa-Levodopa taken by the subject and the use of rescue medication.

9.2.2. Prohibited Medications

Subjects who have used any known strong inhibitors and/or inducers of CYP3A4 within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug are to be excluded from the study; these medications/products are prohibited during the study.

The anticholinergic drug classes listed in Appendix 3 and amantadine are not permitted in the 5 days prior to the admission visit (Day -1) of each part of the study. The list provides non-exhaustive examples of each drug class.

9.3. Treatment Compliance

Study drug (SAGE-217 or matched placebo) will be prepared by the site pharmacist. All doses of study drug will be administered by site staff while the subject is confined to the clinical unit. The Investigator(s) or designee will record the time and dose of study drug administration in the source documents. Any reasons for noncompliance will also be documented, including:

- Missing visits;
- Interruptions in the schedule of administration; and
- Nonpermitted medications.

The time at which study procedures are conducted should follow the protocol timelines as closely as possible.

9.4. Randomization and Blinding

Part A of the study is open-label.

In 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 groups: open-label Levodopa plus blinded SAGE-217 Oral Solution or matching placebo oral solution. Subjects, clinicians, and the study team will be blinded to treatment allocation. The pharmacist, who will prepare the oral solutions 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.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

SAGE-217 Oral Solution is available as a 6 mg/mL stock aqueous solution of SAGE-217 Drug Substance containing 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection to achieve the selected dosages. The 6 mg/mL stock SAGE-217 Oral Solution will be compounded from SAGE-217 Drug Substance Powder in the Bottle and Excipient(s) in the Bottle (manufactured under current Good Manufacturing Practice [GMP] conditions [redacted]) and further admixed at the clinical site in preparation for dosing. Placebo will be matched to SAGE-217 study drug. Detailed instructions for study drug preparation will be provided in the Pharmacy Manual.

The Sponsor will not provide Levodopa or Carbidopa-Levodopa during the study; subjects will use their prescribed Levodopa or Carbidopa-Levodopa.

10.2. Study Drug Packaging and Labeling

The composition and pharmaceutical quality of the investigational product will be maintained according to the current GMP and Good Clinical Practice (GCP) guidelines and available for review in the study medication documentation. Study drug will be provided to the site as powder in the bottle and excipient(s) in the bottle units to be compounded in the pharmacy at a volume of 125 mL of a 6 mg/mL stock solution and then further diluted to approximately 40 mL at the identified doses. Study drug labels with all required information and conforming to all applicable Code of Federal Regulations and GMP/GCP guidelines will be prepared by the clinical research organization.

10.3. Study Drug Storage

Upon receipt of study drug (SAGE-217 Oral Solution and placebo oral solution), the Investigator or designee will inspect the materials and complete and return the acknowledgment of receipt form enclosed with the parcel. A copy of the signed receipt will be kept in the study files.

The study drug materials for SAGE-217 Oral Solution and placebo oral solution must be carefully stored at the temperature specified in the Pharmacy Manual (eg, clinical dosing solutions stored at approximately 2 to 8°C for 11 days with 24 hours of room temperature excursions allowed after preparation), safely and separately from other drugs. The study drug may not be used for any purpose other than the present study. After the study is completed, all unused study drug must be retained, returned as directed, or destroyed on site per the Sponsor's instructions.

The Investigator or designee will be responsible for ensuring appropriate storage, compounding, dispensing, inventory, and accountability of all clinical supplies. An accurate, timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory must be available for inspection by the designated representatives of the Sponsor or the Sponsor's representatives on request, and must include the information below:

- The identification of the subject to whom the drug was dispensed;

- The date(s) and quantity of the drug dispensed to the subject; and
- The product lot/batch number.

The preparation of the study drugs must be documented on a 'Drug Preparation and Dispensing Log Form' or similar form.

A copy of the inventory record and a record of any clinical supplies that have been destroyed must be documented. This documentation must include at least the information below or as agreed with the Sponsor:

- The number of prepared units;
- The number of administered units;
- The number of unused units;
- The number of units destroyed at the end of the study;
- The date, method, and location of destruction.

10.4. Study Drug Preparation

Each bottle of SAGE-217 Oral Solution 6 mg/mL will be compounded at the clinical pharmacy from components manufactured [redacted] and supplied by the Sponsor per the directions provided in the Pharmacy Manual. The batch formula for a 125 mL solution of the 6 mg/mL stock solution is shown in Table 5.

Table 5: Batch Formula for 125 mL of Stock SAGE-217 Oral Solution 6 mg/mL

Ingredient	Compendia Specification	Concentration (mg/mL)	Amount (mg/Bottle)
SAGE-217	not applicable	6	750
HPβCD [redacted]	USP/EP	457	57,100
Sucralose	USP/NF	0.029	3.569
Water for Injection	USP	not applicable	85,650

Abbreviations: EP = European Pharmacopeia; HPβCD = hydroxypropyl-β-cyclodextrin; NF = National Formulary; USP = United States Pharmacopeia

Additional excipients may be utilized in placebo to match the taste of SAGE-217 Oral Solution. They include sucrose octaacetate, tannic acid, and ammonium glycyrrhizate. The quantities may vary depending on the dose of SAGE-217.

10.5. Administration

SAGE-217 Oral Solution or matching placebo will be administered in the morning with food.

Doses of SAGE-217 and placebo for SAGE-217 will be prepared as an approximate 40 mL oral solution to be swallowed all at once, followed by approximately 200 mL of water that has been used to rinse the dosing bottle. The start time of swallowing the approximately 40 mL oral solution is time zero for all assessments. Subjects may have assistance from the clinic staff when taking the study drug.

During Confinement, each subject's antiparkinsonian agents, including Levodopa or Carbidopa-Levodopa, will be administered by site personnel according to the site's standard operating procedures.

10.6. Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator or designee must maintain a record of all study drug received, used, and discarded. It must be clear from the records which subject received which dose of active or placebo treatment.

The Sponsor will be permitted access to the study supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation. Only unblinded personnel will be able to access the study drug and accountability documentation from first dosing through database hard lock.

The Investigator will document all doses of Levodopa or Carbidopa-Levodopa taken by the subject, including rescue doses.

10.7. Study Drug Handling and Disposal

The pharmacist or designee for drug accountability is to document the date and time of initial compounding, subsequent admixture of dosing solutions, administration of study drug, and for which subject the study drug was intended (ie, record subject initials and birth date or other unique identifier).

At the end of the study, any unused study drug will be retained or returned to the Sponsor for destruction or destroyed locally per the Sponsor's directions; disposition of study drug will be documented.

11. ASSESSMENT OF EFFICACY

Efficacy assessments include evaluation of PD symptoms by the MDS-UPDRS, [redacted] Assessments will be perfoimed periodicall y dming the study as outlined in the Schedule of Events (Table 2 and Table 3).

11.1. Movement Disorder Society- Unified Parkinson's Disease Rating Scale

The UPDRS is the the most commonly used scale in clinical studies of PD (Ramaker 2002). In 2007, the MDS revised the scale, which was known as the MDS-UPDRS (Goetz 2007), and subsequently demonstrated the validity of the MDS-UPDRS for rating PD (Goetz 2008). The modified UPDRS includes four scales, with various subscales. Each item is rated from 0 (noimal) to 4 (severe) (Table 6). The four MDS-UPDRS scales are:

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

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

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

Pait IV: Motor complications (6 items)

Table 6: Rating Scale for the MDS-UPDRS

Rating	Description
0 = no1mal	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

Several questions in Pait I and all questions in Pait II can be answered by the patient/caregiver and completed without the Investigator's input. The remaining questions in Pait I that deal with complex behaviors, the objective assessments of parkinsonism (Pait III), and the questions that deal with motor fluctuations and dyskinesias (Pait IV) ai·e co mpleted by In vestigator interview. Th e tim e requ ired for ad m inistering the MDS-UPDRS is estimated to be less than 10 minutes for the interview items of Pait I, 15 minutes for Pait III, and 5 minutes for Pait IV (Goetz 2008).
The complete MDS-UPDRS is to be administered in Pait A at screening, Admission (Day -1), predose on Days 1, 2, 3, and 4; postdose on Day 7; and on Day 14. The complete MDS-UPDRS is to be administered in Pait B at screening, Admission (Day -1), predoseon Days 1 and 4; postdose on Day 8; and on Days 15 and 22.

Pait III of the MDS-UPDRS 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, global spontaneity of movement (Goetz. 2008). Pait III of the MDS-UPDRS (motor examination) is to be completed in Part A at 2, 4, 8, and 12 hours postdose on Days 5, 6, and 8, and in Pait B at 2, 4, 8, and 12 homs postdose on Days 2, 3, 5, 6, 7, and 9. MDS-UPDRS is to be assessed within ±10 minutes of the scheduled times through the 4-hour time point and within ±15 minutes of the scheduled times for the 6-hour through 12-hour time points. The MDS-UPDRS is provided in Appendix 4.

11.2. Exploratory Endpoints

[redacted]

[redacted]

12. PHARMACOKINETICS

12.1. Blood Sample Collection

In Part A, plasma samples for PK analysis will be collected predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Day 4; predose on Day 5 and Day 6; predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Day 7; in AM of Day 8; and Day 14. In Part B, plasma samples for PK analysis will be collected predose and 0.25, 0.5, 1, 2, 4, 8, and 12 hours postdose on Days 1 to 4; 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 the AM on Day 9; and on Days 15 and 22. The time of study drug administration is time zero and all post-dosing sampling times are relative to this time. Samples are to be collected within ±5 minutes of the scheduled sampling time. The Investigator or designee will arrange to have the plasma samples processed, stored, and transported as directed for bioanalysis.

An additional PK sample may be collected at any time if clinically indicated and at the discretion of the Investigator (eg, for unusual or severe adverse events).

Each sample will be marked with unique identifiers such as the study number, subject number, and the nominal sample time. The date and actual time that the blood sample was taken will be recorded on the eCRF or electronically with a bar code or other method.

12.2. Storage and Shipment of Pharmacokinetic Samples

The plasma samples should be kept frozen at approximately -70°C to -80°C until analyzed. They should be packed as directed to avoid breakage during transit and with sufficient dry ice to prevent thawing for at least 72 hours. A specimen-identification form must be completed and sent to the laboratory with each set of samples. The clinical site will arrange to have the plasma samples transported as directed for bioanalysis as detailed in the PK instructions.

12.3. Sample Analysis

Bioanalysis of plasma samples for the determination of concentrations of SAGE-217, SAGE-217 metabolites, and HPβCD will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory. Pharmacokinetic parameters will be derived such as area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to reach maximum concentration (t_{max}), the distributional half-life and terminal half-life ($t_{1/2}$), and steady-state drug concentration in the plasma (C_{ss}).

13. ASSESSMENT OF SAFETY

13.1. Safety and Tolerability Parameters

Safety and tolerability of study drug will be evaluated by adverse event reporting, vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, and SSS and MOAA/S scores.

13.1.1. Demographic/Medical History

Age, gender, race, and ethnic origin will be recorded at the Screening visit for Part A. A full medical history, including PD history (eg, time of diagnosis, staging) and medication history, will be recorded at the Screening visit for Part A and updated, as needed, as screening for Part B.

13.1.2. Vital Signs

Vital signs comprise respiratory rate, temperature, and supine (supine for at least 5 minutes prior to the measurement) and standing systolic and diastolic blood pressure and heart rate.

In Part A, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in AM of Day 8; and on Day 14. In Part B, vital signs and pulse oximetry will be performed at screening (vital signs only) and Admission (Day -1); predose and at 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 8; in AM on Day 9; and on Days 15 and 22. Vital signs and pulse oximetry are to be assessed within ±10 minutes of the scheduled times through the 4-hour time point and within ±15 minutes of the scheduled times for the 6-hour through 16-hour time points.

13.1.3. Weight and Height

Body weight and height will be measured at the Screening visits for Parts A and B.

13.1.4. Physical Examination

A physical examination of all major body systems will be undertaken and recorded at the Screening visits for Parts A and B. Symptom-directed physical examinations will be performed during Part A on Admission (Day -1), Day 1, Day 3, Day 4, Day 6, and Day 8. Symptom-directed physical examinations will be performed during Part B on Admission (Day -1), Day 1, Day 3, Day 4, Day 5, Day 7, Day 8, Day 9, and Day 15.

13.1.5. Electrocardiogram (ECG)

A supine 12-lead ECG will be performed at the times specified below and the standard intervals recorded as well as any abnormalities.

In Part A, the 12-lead ECG will be assessed at screening and Admission (Day -1); predose on Days 1 and 3; predose and 1 and 12 hours postdose on Days 4, 5, 6, and 7; in AM on Day 8; and Day 14. In Part B, the 12-lead ECG will be assessed at screening and Admission (Day -1); predose and 1 and 12 hours postdose on Days 1 through 8; in AM on Day 9; Days 15 and 22.

All time points are relative to the time of dosing. ECGs are to be performed within ±10 minutes of the predose and 1-hour time points and within ±15 minutes of the 12-hour time point.

13.1.6. Laboratory Assessments

In Part A, blood samples will be collected for hematology and serum chemistry at the Screening visit, on Admission (Day -1), predose on Days 4, 6, and 8; and on Day 14. Urine samples will be collected in Part A at screening and Admission (Day -1); predose on Day 4 and Day 7; and on Day 14. In Part B, blood samples will be collected at screening and Admission (Day -1); predose on Days 1, 3, 4, 5, 6, and 8; on Day 9 and Day 15. Urine samples will be collected in Part B at screening and Admission (Day -1); predose on Day 4 and Day 8; and on Day 15.

Serum and urine samples for pregnancy tests (females only) will also be collected. These assessments should be performed in accordance with the Schedule of Events (Table 2 and Table 3) and as outlined individually below.

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS). Screening results considered abnormal, CS recorded at the Screening visit may make the subject ineligible for the study pending review by the Medical Monitor. Clinical laboratory results that are abnormal, CS during the study but within normal range at baseline and/or indicate a worsening from baseline will be considered adverse events, assessed according to Section 13.2, and recorded in the eCRF.

13.1.6.1. Hematology

Hematology tests will include complete blood count (CBC), including red blood cells, white blood cells with differentiation, hemoglobin, hematocrit, reticulocytes, and platelets. The coagulation panel will include activated partial thromboplastin time, prothrombin time, and international normalized ratio.

13.1.6.2. Blood Chemistry

Serum chemistry tests will include serum electrolytes, renal function tests, including creatinine, blood urea nitrogen, bicarbonate or total carbon dioxide, liver function tests, including total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), total protein, and albumin.

13.1.6.3. Urinalysis

Urinalysis will include assessment of protein, blood, glucose, ketones, bile, urobilinogen, hemoglobin, leukocyte esterase, nitrites, color, turbidity, pH, and specific gravity.

13.1.6.4. Virus Serology

Subjects will be screened for hepatitis (HBsAg and anti-HCV) and HIV prior to being enrolled in the study.

13.1.6.5. Pregnancy Screen

Females of childbearing potential will be tested for pregnancy at Parts A and B by serum pregnancy test at the Screening visits and by urine pregnancy test on Day -1 (Admissions).

13.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS)

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

If in the opinion of the Investigator, the subject is showing any suicidal tendency, no further study drug will be administered and the subject will be referred to a psychologist or psychiatrist for further evaluation. This information will be tracked.

The "Baseline/Screening" C-SSRS form will be completed on Screening of Part A (lifetime history and past 24 months). In Part A, the "Since Last Visit" C-SSRS form will be completed on Admission (Day -1); 12 hours postdose on Days 1, 2, and 3; predose on Days 4, 5, 6, and 7; and on Days 8 and 14. In Part B, the "Since Last Visit" C-SSRS form will be completed on Admission (Day -1); 12 hours postdose on Day 1 through Day 8; and on Days 9, 15, and 22. The C SSRS is provided in Appendix 9.

13.1.8. Stanford Sleepiness Scale (SSS)

The SSS is 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'.

In Part A, the SSS will be administered on Admission (Day -1); predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 7; in the AM on Day 8; and Day 14. All time points are relative to the time of dosing. 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. In Part B, the SSS will be administered on Admission (Day -1); predose on Days 1 through 8; in AM on Day 9; and Days 15 and 22. The SSS should be performed prior to the MOAA/S score. The SSS is provided in Appendix 10.

13.1.9. Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S)

The MOAA/S allows exploration of deeper sedation states than the SSS. If an 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. In Part A, the MOAA/S assessment should be conducted after other assessments that are scheduled at the same time point. In Part A, the MOAA/S will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 3, 4, 5, 6, and 7; in AM on Day 8; and Day 14. In Part B, the MOAA/S will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, and 16 hours postdose on Days 1 through 8; in AM on on Day 9; and Days 15 and 22. The MOAA/S 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 for the 6-hour through 16-hour time points. The MOAA/S is provided in Appendix 11.

13.2. Adverse and Serious Adverse Events

Adverse events will be collected after the ICF has been signed. Medical conditions that occur after the ICF has been signed will be captured on the adverse event eCRF.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (version 18.1 or higher).

13.2.1. Definition of Adverse Events

13.2.1.1. Adverse Event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. In clinical studies, an adverse event can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

All adverse events that occur after any subject has been enrolled, before treatment, during treatment, or following the cessation of treatment until the Day 22 Follow-up visit of Part B, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics.

13.2.1.2. Suspected Adverse Reaction

A suspected adverse reaction is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

13.2.1.3. Serious Adverse Event

A serious adverse event is an adverse event occurring during any study phase and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following:

- It results in death
- It is immediately life-threatening
- It requires inpatient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- It results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

All serious adverse events that occur after any subject has been enrolled, before treatment, during treatment, and until the Day 22 Follow-up visit of Part B, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics.

13.2.1.4. Recording Sedation as an Adverse Event

Sedation will be assessed using protocol-specified rating scales. In order to standardize the reporting of sedation as adverse events, Investigators must record sedation as an adverse event if there is a score of >5 on the SSS and/or a score of ≤2 on the MOAA/S. Consideration should be given to the most appropriate term to describe the sedation characteristics.

13.2.2. Pregnancy

Any pregnancy occurring during this study will be reported within 24 hours of notification of the Investigator. The Investigator will promptly notify the Medical Monitor and withdraw the subject from the study. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The Investigator should request permission to contact the subject, the subject's spouse/partner (if the subject is male and his spouse/partner becomes pregnant) or the obstetrician for information about the outcome of the pregnancy (spontaneous miscarriage, elective termination, live birth), and in the case of a live birth, about any congenital abnormalities. If a congenital abnormality is reported, then it should be recorded in the source documents and reported as a serious adverse event. Spontaneous miscarriages should also be reported and handled as serious adverse events. Elective abortions without complications should not be handled as adverse events.

13.3. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each adverse event (unrelated, possibly related or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the adverse event should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the adverse event, then the adverse event should be considered "related."

Not related	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possibly related	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.
Probably related	The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.

If the relationship between the adverse event/serious adverse event and the investigational product is determined to be "possible" or "probable", the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

13.4. Recording Adverse Events

Adverse events spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Clinically significant changes in laboratory values, blood pressure, and pulse need not be reported as adverse events unless they prompt corrective medical action by the Investigator, constitute a serious adverse event or lead to discontinuation of administration of study drug.

Information about adverse events will be collected from the signing of the ICF until the final visit of the study for that subject. Adverse events that occur after the first administration of study drug will be denoted TEAEs.

All adverse events will be followed until they are resolved or have reached a clinical plateau with no expectation of future change.

The adverse event term should be reported in standard medical terminology when possible. For each adverse event, the Investigator will evaluate and report the onset (date and time), resolution or clinical plateau (date and time), intensity, causality, action taken, outcome, and whether or not it caused the subject to discontinue the study.

Intensity will be assessed according to the following scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe adverse events. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 13.2.1.3. An adverse event of severe intensity may not be considered serious.

13.5. Reporting Serious Adverse Events

All serious adverse events (regardless of causality) will be recorded from the signing of the ICF until the Day 22 Follow-up visit of Part B. Any serious adverse events considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All serious adverse events must be reported to the Sponsor or Sponsor's designee immediately by phone and in writing within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the serious adverse event pages, verify the accuracy of the information recorded on the serious adverse event pages with the corresponding source documents, and send a copy to Sage Therapeutics or designee.

Additional follow-up information, if required or available, should be sent to Sage Therapeutics or designee within 24 hours of receipt; a follow-up serious adverse event form should be completed and placed with the original serious adverse event information and kept with the appropriate section of the CRF and/or study file.

Sage Therapeutics or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB of all serious adverse events that occur at his or her site if applicable per the IRB's requirements. Investigators

will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB of these additional serious adverse events.

14. STATISTICAL METHODS AND CONSIDERATIONS

14.1. Data Analysis Sets

The safety population is defined as all subjects who are administered study diug.

The efficacy population will consist of all subjects in the safety population who receive at least one dose of study di1g and have at lea st on e po st dose MDS-UPDRS evaluation.

The PK population will consist of all subjects in the safety population with sufficient plasma concentrations for PK evaluations.

Separate populations will be defined for each pa1t of the study.

14.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All subjects will be used in the analyses, as per the analysis populations, using all non-missing data available. No imputation process will be used to estimate missing data. No sensitivity analysis of missing data will be perfo1med.

14.3. Demographics and Baseline Characteristics

Demographics, such as age, gender, race, and ethnicity, and baseline characteristics, such as height, weight, and body mass index (BMI), will be summarized.

Categorical summaries, such as gender and race, will be summarized by frequency and percentage. Continuous summaries, such as age, height, weight, BMI, and baseline vital signs, will be summarized using descriptive statistics.

Hepatitis, HIV, and pregnancy screening results will be listed, but not summarized as they are considered pait of the inclusion/exclusion criteria.

Medical histo1y will be listed by subject.

14.4. Efficacy Endpoints

The primary endpoints of this study relate to safety and tolerability. Efficacy assessments include evaluation of PD s n toms b the MDS-UPDRS, [redacted]

14.4.1. Secondary Efficacy Endpoints

In Pait A, changes in the MDS-UPDRS - Pait III score will be summaii·zed overall and by tolerated dose. In Pait B, changes in the MDS-UPDRS-Pa1t III score and the MDS-UPDRS - Paits I-IV total score will be sUffiln ai·ized overall and by randomized treatment sequence and tolerated dose.

14.4.2. Exploratory Efficacy Endpoints

[redacted]

[redacted]

14.5. Safety and Tolerability Analyses

Data from vital signs, clinical laboratory measures, ECG, C-SSRS, SSS, and MOAA/S will be summarized using descriptive statistics by group and time point, where applicable. Continuous endpoints will be summarized with number (n), mean, standard deviation, median, minimum, and maximum. In addition, change from baseline values will be calculated at each time point and will be summarized using descriptive statistics. Out-of-range safety endpoints may be categorized as low or high, where applicable. For all categorical endpoints,summaries will include counts and percentages.

14.5.1. Adverse Events

Adverse events will be coded using the MedDRA coding system (version 18.1 or higher). The analysis of adverse events will be based on the concept of TEAEs. A TEAE is defined as an adverse event with onset after the start of open-label study drng, or any worsening of a pre-existing medical condition/adverse event with onset after the strut of open-label study chug and until 14 days after the last dose. The incidence of TEAEs will be summarized overall and by MedDRA System Organ Class, preferred tenn, and dose group. Incidences will be presented in order of decreasing frequency. In addition, summaii·es will be provided by maximum severity (see Section 13.4) and relationship to study chug (see Section 13.3).

Treatment-emergent adverse events leading to discontinuation and serious adverse events (see Section 13.2.1.3 for definition) with onset after the first dose of open-label study chu g w ill also be summaii·zed.

All adverse events and serious adverse events (including those with onset or worsening before the strut of open-label study chu g) thro ugh the Day 22 Follow-up visit of Pait B will be listed.

14.5.2. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from baseline of Pait A and Pait B in vital signs will be evaluated by time point.

14.5.3. Physical Examinations

Screening physical examination results for Pait A and Pait B will be listed by subject. Any clinically significant physical exainination will be recorded in medical histo1y . Physical examination findings will be listed by subject and visit; abno lmal findings will be flagged on the listing.

14.5.4. 12-Lead ECG

The following ECG parameters will be listed for each subject: heart rate, PR, QRS, QT, QTc, and QTcF. Any clinically significant abnormalities or changes in ECGs should be listed as an adverse event. Electrocardiogram findings will be listed by subject and visit.

14.5.5. Clinical Laboratory Evaluations

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline of Parts A and B in clinical laboratory measures will be summarized.

14.5.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

Suicidality data collected on the C-SSRS will be listed for all subjects. Listings will include behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

14.5.7. Stanford Sleepiness Scale (SSS)

Sedation data collected on the SSS will be listed for all subjects. Changes in score over time will be represented graphically, and change from baseline of Part A and Part B will be summarized.

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

Sedation data collected on the MOAA/S will be listed for all subjects. Changes in score over time will be represented graphically, and change from baseline of Part A and Part B will be summarized.

14.5.9. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and will be coded using World Health Organization (WHO)-Drug dictionary September 2015, or later.

Medications will be presented according to whether they are being taken prior to and/or during the study (concomitant). Prior medications are defined as those taken during the 4 weeks prior to the date of the first dose of open-label study drug. Concomitant medications are defined as those with a start date on or after the first dose of open-label study drug, or those 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. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Concomitant medications will be assigned to the study part in which they are being taken. 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.

The use of rescue medication will be recorded and summarized.

14.6. Pharmacokinetic Analysis

Phaimacokinetic parameters will be summarized using appropriate descriptive statistics. Time to reach maximum concentrntion (tma.x) will be summarized using number (n), mean, standai·d deviation, median, minimum, and maximum. All other PK pai·ameters will be summarized using n, geometric mean, coefficient of vaii·ation, median, minimum, and maximum and listed by subject.

Wherever necessaiy and appropriate, PK pai·aineters will be dose-adjusted to account for individual differences in dose.

[redacted] Additional exposure-response analyses may be perfo1med for other measures of efficacy and safety.

14.7. Determination of Sample Size

Approximately 18 subjects will be enrolled in Pait A. An interim analysis is planned after 10 subjects have completed Pait A through Day 14. Approximately 12 subjects are anticipated to be randomized to Part B. This number of subjects is thought to be sufficient to assess preliminaiy safety and tolerability as well as a signal of efficacy of SAGE-217 Oral Solution in subjects with PD.

14.8. Changes From Protocol Specified Analyses

Any changes from the analytical methods outlined in the protocol will be documented in the final statistical analysis plan.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of <Sponsor> will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sage Therapeutics or designee or its representatives. This will be documented in a Clinical Study Agreement between Sage Therapeutics and the Investigator.

During the study, a monitor from Sage Therapeutics or designee will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s);
- Confirm that facilities remain acceptable;
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (eg, clinic charts);
- Record and report any protocol deviations not previously sent to Sage Therapeutics or designee; and
- Confirm adverse events and serious adverse events have been properly documented on eCRFs and confirm any serious adverse events have been forwarded to Sage Therapeutics or designee and those serious adverse events that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

15.2. Audits and Inspections

Authorized representatives of Sage Therapeutics, a regulatory authority, an Independent Ethics Committee (IEC) or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sage Therapeutics or designee audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Council on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency about an inspection.

15.3. Institutional Review Board (IRB)

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator and institution will permit study-related monitoring, audits, IRB review, and regulatory inspections as requested by Food and Drug Administration, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (ie, original medical records, laboratory reports, hospital documents, progress reports, signed ICFs) in addition to eCRFs.

Quality assurance and quality-control systems with written standard operating procedures will be followed to ensure this study will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality-assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements made by the Sponsor with the Investigator/institution and any other parties involved with the clinical study will be in writing in a separate agreement.

17. ETHICS

17.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Sage Therapeutics or designee before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Sage Therapeutics or designee will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

17.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and the most recent amendment (2008) and are consistent with ICH/GCP and other applicable regulatory requirements.

17.3. Written Informed Consent

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

18. DATA HANDLING AND RECORDKEEPING

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

Electronic case report forms will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, and subject status.

The Investigator will have access to the electronic data capture system and will receive a copy of the subject eCRF data at the end of the study. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

18.1. Inspection of Records

Sage Therapeutics or designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

18.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Sage Therapeutics or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

18.3. Confidentiality

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available study registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used

towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

19. PUBLICATION POLICY

All information concerning SAGE-217 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

20. LIST OF REFERENCES

Belelli D, Casula A, Ling A, Lambert JJ. The influence of subunit composition on the interaction of neurosteroids with GABA(A) receptors. Neurophan nacology. 2002 Sep;43(4):651- 61.

[redacted]

Bergman H, Deuschl G. Pathophysiology of Parkinson's disease: from clinical neurology to basic neuroscience and back. Mov Disord. 2002;17:S28-S40.

[redacted]

di Michele F, Longone P, Romeo E, et al. Decreased plasma and cerebrospinal fluid content of neuroactive steroids in Parkinson's disease. Neurol Sci. 2003;24(3):172-3.

Goetz CG, Poewe W, Rascol 0 , et al. Movement Disorder Society Task Force Report on the Hoehn and Yalu Staging Scale: Status and Recommendations. Mov Dis. 2004;19(9):1020- 8.

Goetz CG, Fahn S, Maitinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, fonnat, and clinimetric testing plan. Mov Disord. 2007;22(1):41-4 .

Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Pai·kinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. Mov Disord. 2008;23(15):2129-70.

Hoehn M, Yahr M. Parkinsonism: onset, progression and mo1tality. Neurology. 1967;17(5):427-42.

[redacted]

Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Pai·kinson's disease. A clinico-pathological study of 100 cases. JNNP. 1992;55:181-4.

Jankovic J. Moto r fluctuations and dyskinesia in Parkinson's disease: Clinical manifestations. Mov Disord. 2005;11:ll -6.

Jankovic J. Parkinson's' disease: clinical features and diagnosis. JNNP. 2008;79:368-76.

Kasten M, Brnggemann N, Schmidt A, Klein C. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology. 2010;75 (5):478-9.

[redacted]

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.

Pritchett DB, Sontheimer H, Shivers BD, et al. Importance of a novel $GABA_A$ receptor subunit for benzodiazepine pharmacology. Nature. 1989;338(6216):582-5.

Ramaker C, Marinus J, Stiggelbout AM, et al. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. Mov Disord. 2002;17(5):867–76.

Siderowf A, Lang AE. Pre-motor Parkinson's disease; concepts and definitions. Mov. Disord 2012;27, 608-16.

Stern MB. Dopamine agonists modify the course of Parkinson disease. Arch Neurol. 2004;61:1969-71.

Weiner WJ. Initial treatment of Parkinson disease: levodopa or dopamine agonists. Arch Neurol. 2004;61:1966-9.

Winkler C, Bentlage C, Nikkhah G, et al. Intracranial transplants of GABA-rich striatal tissue induce behavioral recovery in the rat Parkinson model and promote the effects obtained by intrastriatal dopaminergic transplants. Exp. Neurol. 1999;155:165-186.

21. APPENDICES

Copies of scales and questionnaires included in the following appendices are for reference only; the rating scales and questionnaires reproduced in the eCRFs are to be used for actual subject assessment per the Schedule of Events.

APPENDIX 1. UNITED KINGDOM BRAIN BANK CRITERIA

UK PARKINSON'S DISEASE SOCIETY BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA*

Step 1. Diagnosis of Parkinsonian Syndrome

- Bradykinesia
- At least one of the following
  - Muscular rigidity
  - 4-6 Hz rest tremor
  - postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease

- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

**From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181-184.*

APPENDIX 2. HOEHN AND YAHR STAGING CRITERIA

The Hoehn and Yahr scale, a commonly used system for describing how the symptoms of Parkinson's disease progress, was first published in 1967 (Hoehn 1967). The original scale included 5 disease stages, numbered 1 to 5. The scale was later modified to include two intermediate stages (Goetz 2004).

Original Hoehn and Yahr Scale

Stage 1	Unilateral involvement only, usually with minimal or no functional disability
Stage 2	Bilateral or midline involvement without impairment of balance
Stage 3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent
Stage 4	Severely disabling disease; still able to walk or stand unassisted
Stage 5	Confinement to bed or wheelchair unless aided

Modified Hoehn and Yahr Scale

Stage 0	No signs of disease
Stage 1	Symptoms are very mild; unilateral involvement only
Stage 1.5	Unilateral and axial involvement
Stage 2	Bilateral involvement without impairment of balance
Stage 2.5	Mild bilateral disease with recovery on pull test
Stage 3	Mild to moderate bilateral disease; some postural instability; physically independent
Stage 4	Severe disability; still able to walk or stand unassisted
Stage 5	Wheelchair bound or bedridden unless aided

APPENDIX 3. ANTICHOLINERGIC DRUGS

The following drugs are not permitted in the 5 days prior to receiving the first dose of study drug in Part A and Part B. The list below gives a non-exhaustive list of examples of each drug class.

A. Antimuscarinic agents

Atropine	Benzatropine	Biperiden	Chlorpheniramine
Dicyclomine	Dimenhydrinate	Diphenhydramine	Doxepin
Doxylamine	Glycopyrrolate	Hydroxyzine	Ipratropium
Orphenadrine	Oxitropium	Oxybutynin	Tolterodine
Tiotropium	Trihexyphenidyl	Scopolamine	Solifenacin
Tropicamide			

Tricyclic antidepressants (amitriptyline, clomipramine, doxepin, imipramine, trimipramine, amoxapine, desipramine, nortriptyline, protriptyline)

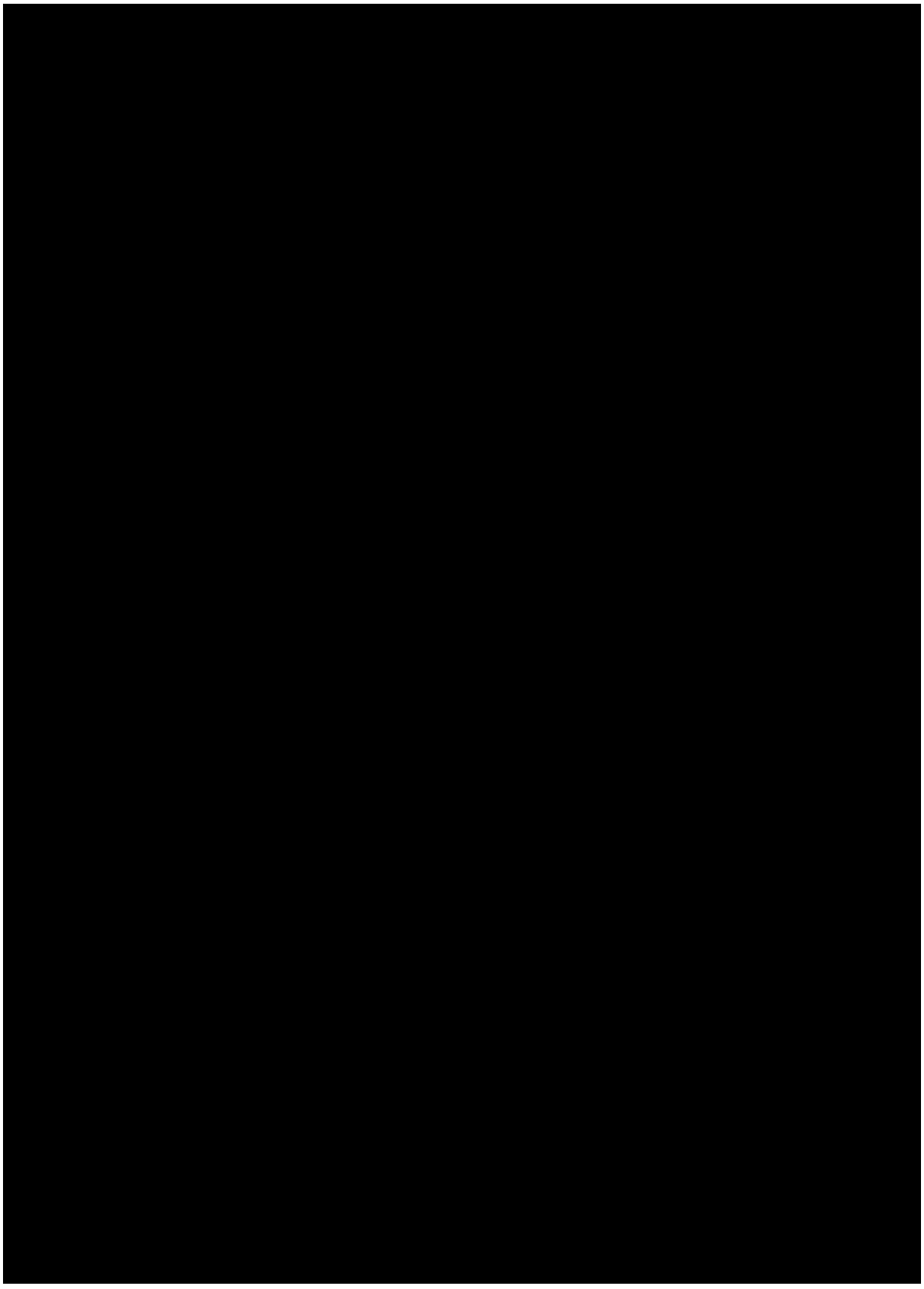
B. Antinicotinic agents:

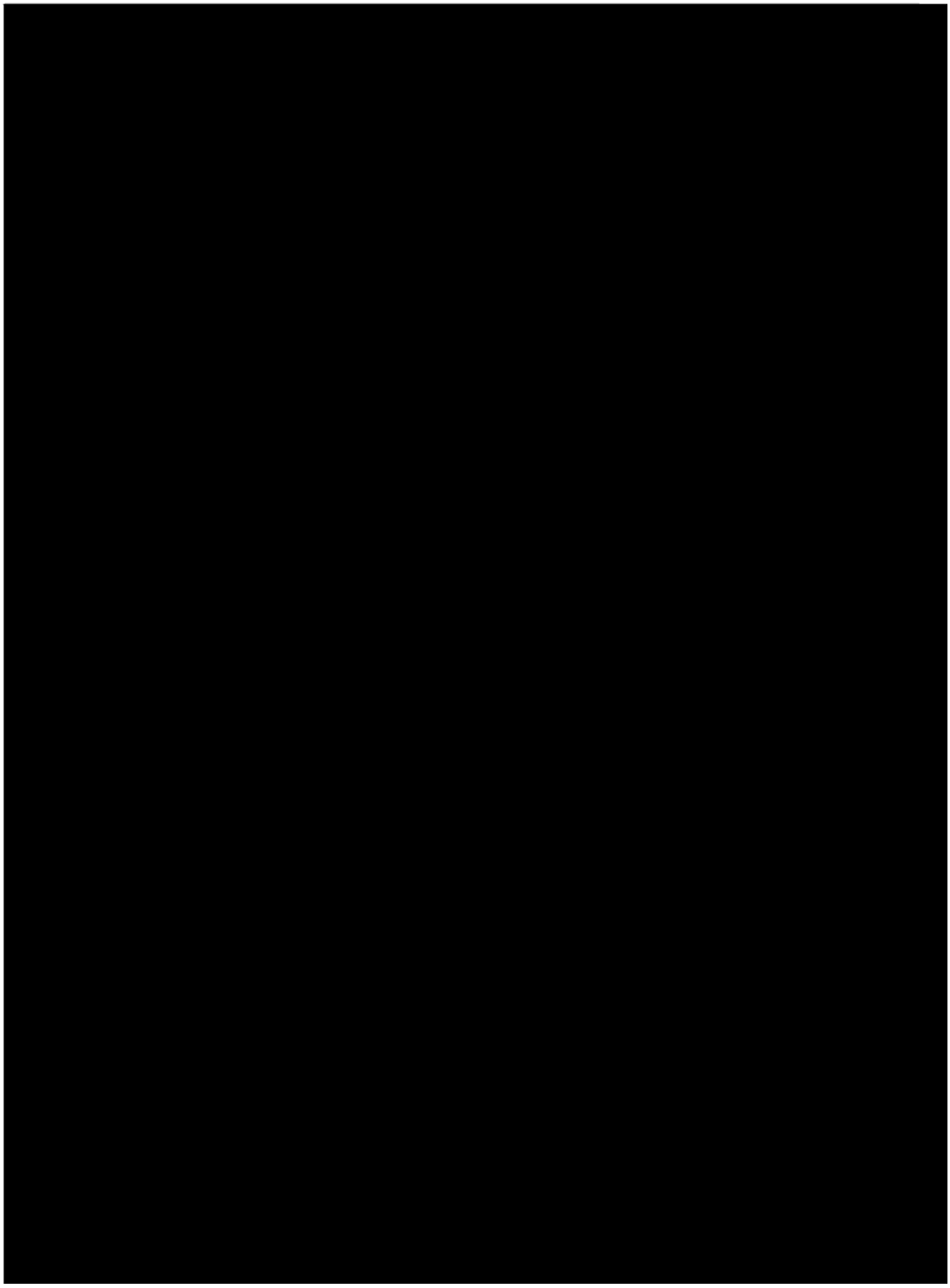
Bupropion	Dextromethorphan	Doxacurium	Hexamethonium
Mecamylamine	Tubocurarine		

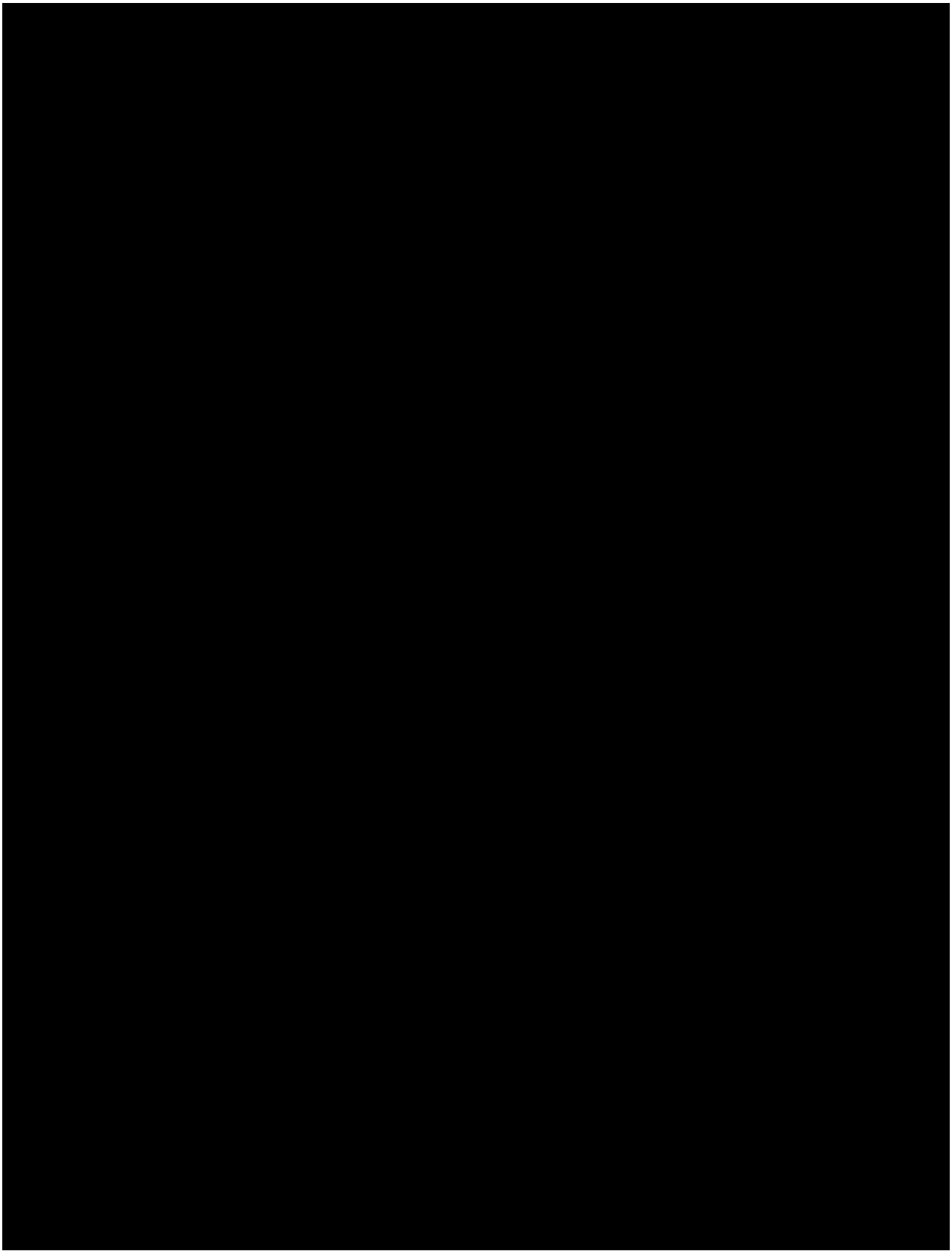
APPENDIX 4. MOVEMENT DISORDER SOCIETY-UNIFIED PARKINSON'S DISEASE RATING SCALE (MDS-UPDRS)

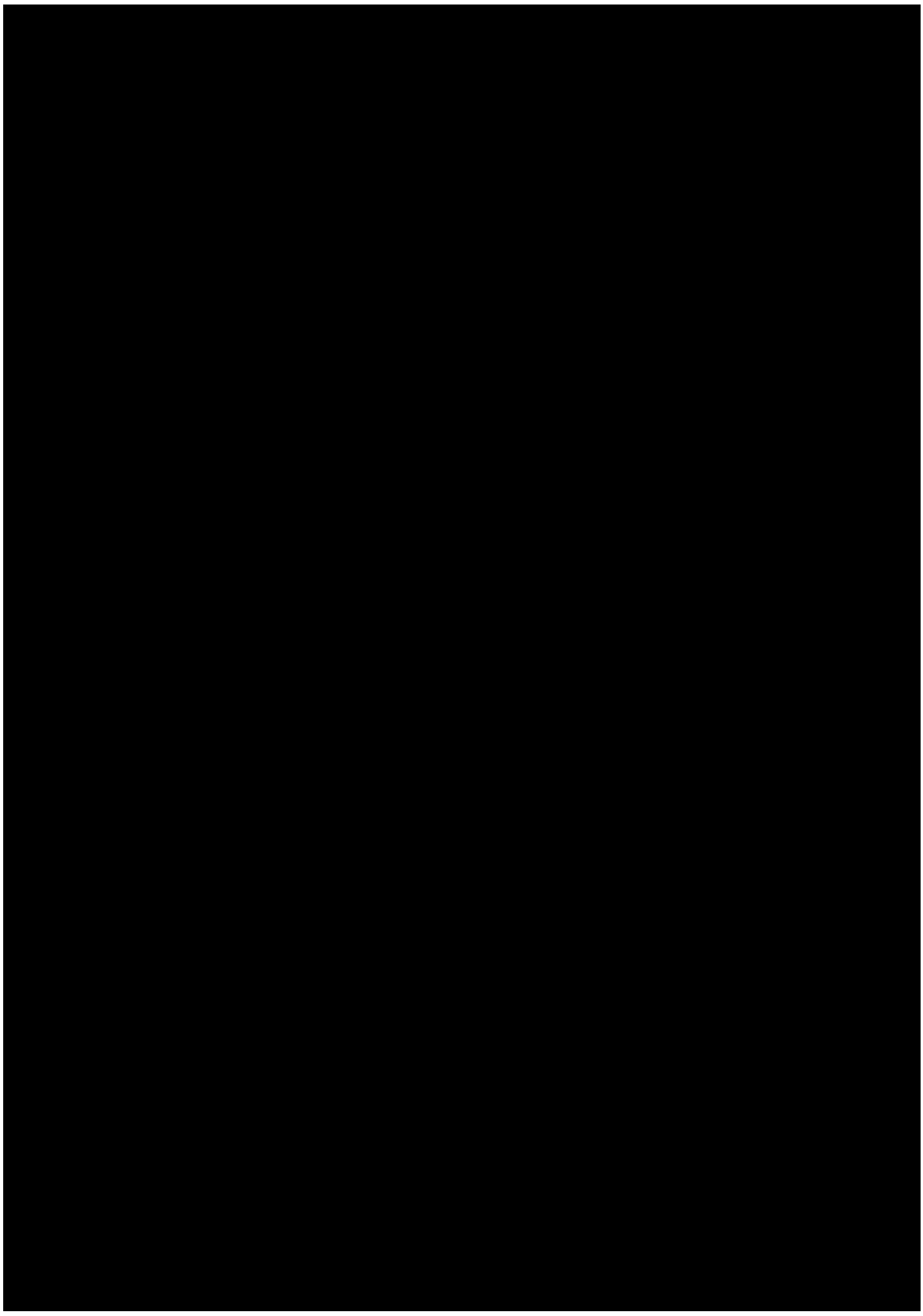
Part I: Nomnotor Aspects of Experiences of Daily Living	**Part II: Moto1· E xp e 1·ien ces of Dail y Li vi ng**
Cogniti ve impairment	Speech
Hallucinations and psychosis	Saliva and drooling
Depressed mood	Chewing and swallowing
Anxious mood	Eating tasks
Apathy	Dressing
Features of dopamine dysregulation syndrome	Hygiene
Sleep problems	Handwriting
Daytime sleepiness	Doing hobbies and other activities
Pain and other sensations	Turning in bed
Urinary problems	Tremor impact on activities
Constipation problems	Getting in and out of bed
Lightheadedness on standing	Walking and balance
Fatigue	Freezing
Part III: Motor Examination	**Part IV : Motor Complications**
Speech	Time spent with dyskinesias
Facial expression	Functional impact of dyskinesias
Rigidity **(neck;** right/left upper/lo wer extremities)	Painful *off* state dystonia
Finger tapping (right/left hands)	Time spent in the *off* state
Hand movements (right/left hands)	Functional impact of fluctuations
Pronation-supination movements of right/left hands	Complexity of motor functions
Toe tapping (right/left foot)	
Leg agility (right/left leg)	
Arising from chair	
Gait	
Freezing of gait	
Postural instability	
Posture	
Global spontaneity of movement (body bradykinesia)	
Postural tremor of right/left hands	
Kinetic tremor of right/left hands	
Rest tremor amplitude: right/left upper/lower extremities; lip jaw	
Constancy of rest tremor	

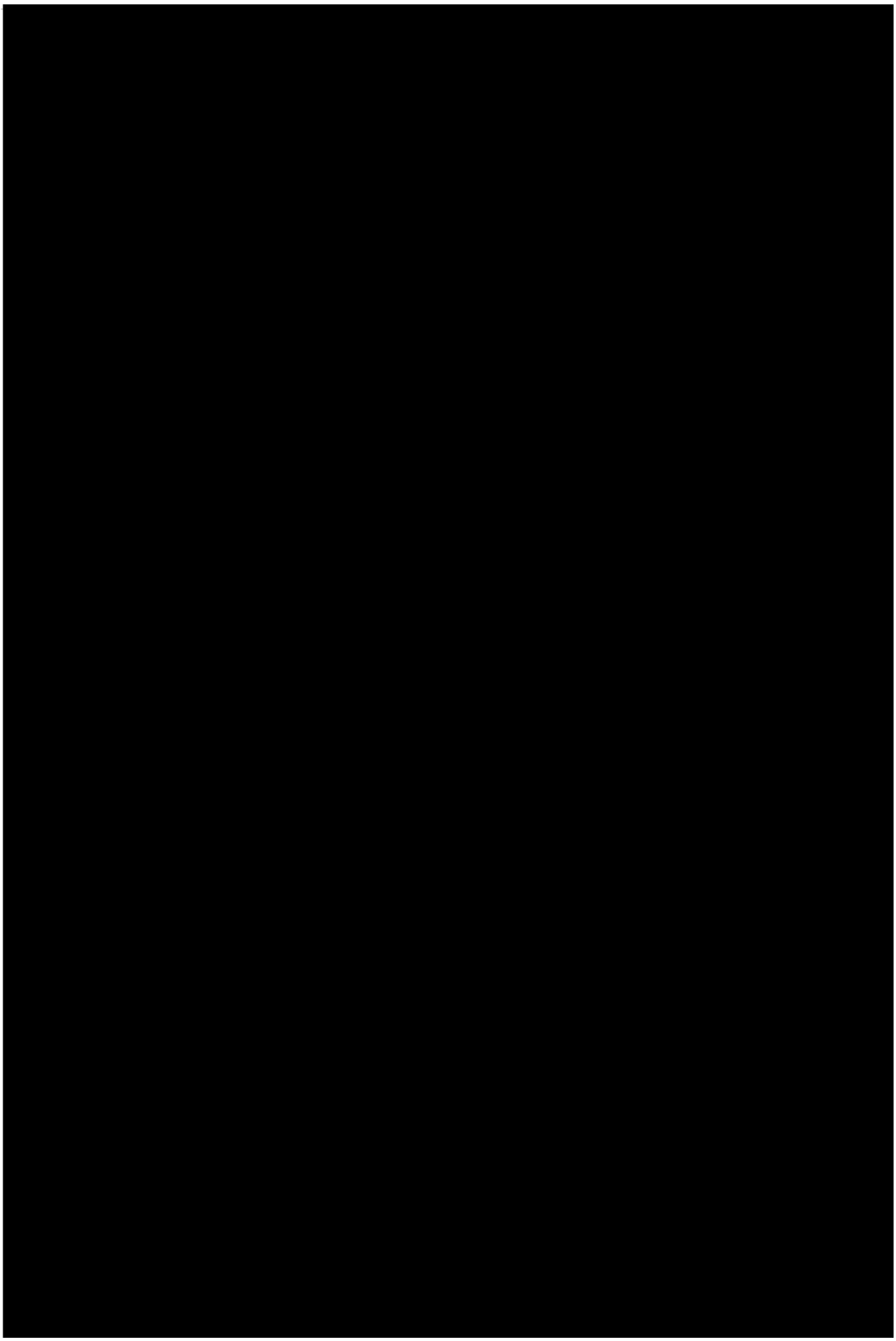
[redacted]











APPENDIX 9. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) – BASELINE/SCREENING VERSION AND SINCE LAST VISIT VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime: Time He/She Felt Most Suicidal
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. *Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?* If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX 10. STANFORD SLEEPINESS SCALE (SSS)

This is a quick way to assess how alert you are feeling. If it is during the day when you go about your business, ideally you would want a rating of a one. Take into account that most people have two peak times of alertness daily, at about 9 a.m. and 9 p.m. Alertness wanes to its lowest point at around 3 p.m.; after that it begins to build again. Rate your alertness at different times during the day. If you go below a three when you should be feeling alert, this is an indication that you have a serious sleep debt and you need more sleep.

An Introspective Measure of Sleepiness
The Stanford Sleepiness Scale (SSS)

Degree of Sleepiness	**Scale Rating**
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X

APPENDIX 11. MODIFIED OBSERVER'S ASSESSMENT OF ALERTNESS/SEDATION (MOAA/S)

Modified Observer's Assessment of Alertness/Sedation Scale

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

March I0, 2017

217-PRK-201 Protocol Administrative Letter #01

This administrative letter is to clarify the following in Protocol 217-PRK-201 Version 3.0 dated 24 October 2016 (Amendment 2):

- Timepoints of the Montreal Cognitive Assessment (MoCA) Table 2 (Part A) footnote "l" and Table 3 (Part B) footnote "l": TheMoCA should be conducted in Part A on Days 1, 3, and 4 and in Part Bon Days 1, 4, and 9, two (2) hours post dose ±30 minutes. All other timepoints on days not specified herein can be administered at any time.

- End of Study Visit for subjects who tenninate early in Pa1i A or Part B: Section 8.4 (page 39), Subject Withdrawal Criteria, states that any subject who is withdrawn from the study for any reason is to have the final visit assessments performed. Final visit assessments for Part A are the assessments for the day of early termination (Days 1-8) plus any additional assessments required for Day 14 (only assessments that are not collected under the assessments on the day of early tennination). If early termination occurs on Part A Days 9-14, then Day 14 is the Final Visit. Final visit assessments for Part B are the Part B, Day 15 assessments. If a subject tenninates early on Part B Days 16-22 then EOS Day 22 is the Final Visit.

- Table 2 (Pa1i A) Row 8 and Table 3 (Part B) Row 6 is identified as "CBC/Semm Chemistry": *This* refers to Hematology and Blood Chemistry as described in Sections 13.1.6.1 and 13.1.6.2 of the Protocol.

- Section 13.1.6.3. Urinalysis (page 53) states "Urinalysis will include assessment of protein, blood, glucose, ketones, bile, urobilinogen, hemoglobin, leukocyte esterase, nitrites, color, turbidity, pH, and specific gravity." Bile is used as a synonym for bilimbin; urine bilirubinshould be tested as part of the urinalysis.

- In Part A on Day -1 duplicate samples are to be collected for Hematology, Blood Chemistry and Urinalysis with one set of samples being sent to a

local lab for confirmationof eligibility based on results prior to dosing on Day I and on a second set of samples being sent to the central lab for analysis.

These clarifications will be included in a future amendment to the protocol.

[redacted] MD

[redacted], MD, MPH

[redacted]

Sage Therapeutics

May24,2017

217-PRK-201 Protocol Administrative Letter #02

This administrative letter is to give you a quick update on SAGE 217-PRK-201 clinical study. You will recall that this study had two phases: Part A and Part B. An interim analysis was conducted on twelve subjects after they completed their dosing in Part A to inform the methodology and conduct of Part B.

In the five subjects with overt tremor (tremor score over five at baseline), an approximate 20-30% improvement in tremor symptoms was observed on the four days of SAGE-217 open-label treatment, as assessed by change in the MDS-UPDRS Part III tremor score. This improvement in tremor score during the SAGE-217 dosing phase was longer-lasting than the effect on tremor observed in these subjects during the levodopa/carbidopa-only phase. Administration of SAGE-217 during the day was found to be generally well-tolerated with no serious adverse events or discontinuations reported. Similar to findings in the Phase I clinical program, the most common adverse events were sedation and somnolence (occurring 2 to 4 hours post dose). While dosing was initiated at the 30 mg per day maximum tolerated dose established in the Phase **1** program, the majority of patients were down-titrated to 10 or 20 mg of SAGE-217 per day.

Based on the signal of activity in reducing Parkinsonian tremor in these patients, Sage plans to proceed to an open-label Part B study evaluating SAGE-217 as an adjunctive treatment to anti-Parkinsonian agents in tremor-predominant patients.

As a result, Part B of this study has been revamped to include the following **key** eligibility criteria:

1. Subjects with PD, who meet the criteria for Hoehn & Yahr stage 1-4 assessed during the "on" period, andhave a tremor with a total score of 2::.10 (sum ofMDS-UPDRS Part 2 and 3 tremor items: 2.10, 3.15, 3.16, 3.17 and 3.18) AND a score 2::.3 in one lim b (from items 3.15, 3.16, or 3.17) AND a constancy of rest tremor score of 2::.3 (item 3.18). Inclusion criteria tremor scores must be assessed during "on" periods assumed to be within 2 hours of dosing with antiparkinsonian agent(s) during the screening and Day -1 visit.
2. Subjects will continue on their stable dose(s) of antiparkinsonian agent(s) and will receive Sage-217 capsules oral once a day at night time for a

period of 7 days. Subjects will receive SAGE-217 capsules 20 mg total dose on Days 1 and 2 and if tolerated, the total daily dose will be escalated to 30 mg on Day 3.

Based upon the tremor scores in the first 12 subjects at admission for Part A of the study, it is unlikely that these subjectswill qualify for the revised Part B. To the extent subjects from Part A meet the aforementioned key entry criteria for the amended Part B, they remain eligible. Please assess these subjects for their tremor scores during the "on" period. If the subject does not meet these criteria, they are ineligible for Part B.

These clarifications will be included in a future amendment to the protocol.

[redacted], MD, MPH
[redacted]
Sage Therapeutics

August 2, 2017

217-PRK-201 Protocol Administrative Letter #03

This memo is to clarify the following:

- Pharmacokinetic sample storage conditions
- Errors in Table 3: Schedule of Events: Part B (Open-Label)
  - MDS-UPDRS Complete
  - MDS-UPDRS Part II only and Part ill only
  - Footnote "p"
  - Footnote "q"

Section 12.2 of Protocol 217-PRK-201, Amendment 4, Version 5.0 states that plasma samples should be kept frozen at approximately -70°C to -80°C until analyzed. This letter defines an acceptable range of -l 5°C to -30°C for sample storage prior to being shipped for bioanalysis.

MDS-UPDRS Complete is to be done in the morning on Day l (8:00 AM ±1 hour) and Day 8 (approximately 12 hours ±15 minutes after the Day 7 dose). MDS-UPDRS Parts II & III are to be done on Days 2, 3, 4, 5, 6, and 7 in the morning and evening at approximately 12 and 23 hours (±15 minutes) following the SAGE-217 dose from the previous Day.

Footnote "p" which corresponds to the PDSS-2 does not reference a Screening timepoint. This is correctly marked with an "X" in Table 3. The PDSS-2 should be done at Screening, on Day l at 8:00 AM (1 hour), Day 8 (12 hours ±15 minutes post Day 7 dose), and on Day 14.

Footnote "q" which corresponds to the BDI-11 incorrectly lists Admission (Day -1). The BDI-11 should be done at Screening and on Days 1, 8, and 14.

[redacted]
MD
Sage Therapeutics