Official Title: A Phase 2A, Double-blind, Placebo-controlled, Randomized Withdrawal Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of SAGE-217 in the Treatment of Subjects with Essential Tremor (ET)

NCT Number: NCT02978781

Document Date: Protocol Version 5- 05 September 2017

1. PROTOCOL AND AMENDMENTS

Protocols and amendments

- Protocol V5.0 Amendment #4 dated 05Sep2017
- Protocol V4.0 Amendment #3 dated 28Apr2017
- Protocol V3.0 Amendment #2 dated 27Jan2017
- Protocol V2.0 Amendment #1 dated 28Oct2016
- Protocol V1.0 dated 19Aug2016

Protocol Number: 217-ETD-201

A Phase 2A, Double-blind, Placebo-controlled, Randomized Withdrawal Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of SAGE-217 in the Treatment of Subjects with Essential Tremor (ET)

IND Number: 131,258

Investigational Product	SAGE-217
Clinical Phase	2a
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted], M.S.H.S. [redacted] Phone: [redacted] Email: [redacted]
Medical Monitor	[redacted], M.D., M.P.H. Study Physician Phone: [redacted] Email: [redacted]
Date of Original Protocol	Version 1.0, 19 August 2016
Date of Amendment 1	Version 2.0, 28 October 2016
Date of Amendment 2	Version 3.0, 27 January 2017
Date of Amendment 3	Version 4.0, 28 April 2017
Date of Amendment 4	Version 5.0, 05 September 2017

PROTOCOL SIGNATURE PAGE

Protocol Number:	217-ETD-201
Product:	SAGE-217
IND No.:	131,258
Study Phase:	2a
Sponsor:	Sage Therapeutics
Date of Amendment 4:	Version 5.0, 05 Sep 2017

Sponsor Approval

[redacted] MD — 05 SEP 2017

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

Sage Therapeutics

[redacted] — 05 Sept 2017

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

Sage Therapeutics

[redacted] — 05 Sep 2017

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

Sage Therapeutics

[redacted] — 05 Sep 2017

[redacted] M.S. — Date (DD/MMM/YYYY)

Sage Therapeutics

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the Clinical Protocol 217-ETD-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
Sponsor Physician	[redacted], M.D., M.P.H. [redacted] Sage Therapeutics [redacted]	215 First Street, Suite 220 Cambridge, MA 02142 Cell: [redacted]
Sponsor Signatory	[redacted], M.D., Ph.D. [redacted] [redacted]	215 First Street, Suite 220 Cambridge, MA 02142 Office: [redacted] Cell: [redacted]
[redacted] Medical Monitor	[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 2a, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of SAGE-217 in the Treatment of Subjects with Essential Tremor (ET)

Study center(s): Up to 25 centers

Phase of development: 2a

Methodology:

This study will assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of SAGE-217. Subjects who consent prior to the approval of Protocol Amendment #3 by the IRB will receive the oral solution formulation for the duration of the study. Subjects who consent after Amendment #3 is approved by the IRB will receive the capsule formulation for the duration of the study.

There are three parts:

Part A: Open-label with morning dosing (7 days).

A screening period to determine subject eligibility will occur between Day -28 to Day -1. All eligible subjects will start on a 10-mg dose of study drug administered with food on Day 1. Subjects will receive 20 mg with food on Day 2 and 30 mg with food daily on Days 3 to 7.

Part B: Double-blind, placebo-controlled, randomized withdrawal with morning dosing (7 days).

In order to qualify for Part B of the study, a subject must tolerate a dose of at least 10 mg of SAGE-217, and the subject must have responded to SAGE-217, defined as a 30% reduction from baseline in the TRG Essential Tremor Rating Assessment Scale (TETRAS) kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) predose on Day 8.

Eligible subjects will be randomized in a 1:1 fashion to SAGE-217 or placebo and will receive their maximum dose as determined in Part A in the morning with food. Subjects randomized to the placebo arm will represent randomized withdrawal (withdrawal from treatment they received in Part A).

Subjects will be exposed to study drug (SAGE-217 or placebo) for up to 14 days and will be followed for an additional 14 days after the administration of the last dose.

Part C: Open-label with evening dosing (14 days). Subjects in Part C will not have participated in Part A or Part B.

A screening period to determine subject eligibility will occur between Day -28 to Day -1. All eligible subjects will start on a 10-mg dose of study drug administered with food in the evening (8:00pm ±30 min) on Day 1. Subjects will receive 20 mg with food in the evening on Day 2, and 30 mg with food in the evening on Day 3. Beginning on Day 4 and continuing through Day 14, subjects will receive a 40-mg total daily dose (administered as 10 mg with food in the morning [8:00am ±30 min] and 30 mg

with food in the evening [8:00pm ±30 min]). Study drug will be self-administered by subjects on an outpatient basis for the entire 14-day Treatment Period. Compliance with study drug administration will be monitored via a follow-up call from the site each evening (within approximately 1 hour following the scheduled evening dose) on Days 1-14.

Subjects will be exposed to study drug (SAGE-217) for up to 14 days and will be followed for an additional 14 days after the administration of the last dose.

Dose adjustments will only be allowed during the open-label phases of the study (Parts A and C). See Section 9.3 for dose adjustment criteria.

Assessments will be performed periodically during Parts A, B, and C, as outlined in the Schedule of Events (Table 2, Table 3, and Table 4, respectively).

Objectives and Endpoints:

Primary Efficacy:

- For Parts A and B, the primary efficacy objective is to compare the effect of 7 days administration of SAGE-217 Capsules to placebo on the change in tremor severity, as measured by the change from randomization (Day 8) in the accelerometer-based Kinesia™ kinetic tremor combined score (ie, the sum of Kinesia kinetic tremor scores from both sides of the body) at Day 14.
- For Part C, the primary efficacy objective is to assess the effect of 14 days administration of SAGE 217 Capsules on tremor severity, as measured by the change from baseline (Day 1) in the accelerometer-based Kinesia™ upper limb tremor combined score (ie, the sum of accelerometer-based Kinesia forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores from both sides of the body) at Day 15.

Secondary Efficacy:

- For Parts A and B, the secondary efficacy objectives are to compare the effect of 7 days administration of SAGE-217 Capsules to placebo (Part A) and to assess the effect of 14 days administration of SAGE-217 Capsules (Part B) on the following endpoints:
  - Tremor severity, as assessed by the change from randomization (Day 8) in the Kinesia upper limb total score (ie, the sum of accelerometer-based Kinesia forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores from both sides of the body) and individual item scores at Day 14.
  - Tremor severity, as measured by the change from randomization (Day 8) in the TETRAS upper limb total score (ie, the sum of TETRAS Performance Subscale item 4 scores [4a, 4b, and 4c] from both sides of the body) and individual TETRAS Performance Subscale upper limb item scores at Day 14.
  - Tremor severity, as assessed by the change from randomization (Day 8) in other TETRAS Performance Subscale scores measured at Day 14.

The above endpoints may also be assessed for SAGE-217 Oral Solution if sufficient data are available.

- For Part C, the secondary efficacy objectives are to assess the effect of 14 days administration of SAGE-217 Capsules on the following endpoints:
  - Tremor severity, as assessed by the change from baseline (Day 1) in the Kinesia upper limb individual item scores at Day 15.
  - Tremor severity, as measured by the change from baseline (Day 1) in the TETRAS upper limb total score (ie, the sum of TETRAS Performance Subscale item 4 scores [4a, 4b, and 4c] from both sides of the body) and individual TETRAS Performance Subscale upper limb item scores at Day 15.

- Tremor severity, as assessed by the change from baseline (Day 1) in the total TETRAS Performance subscale score and other TETRAS Performance Subscale scores measured at Day 15.

Safety:

Safety and tolerability, as assessed by vital signs measurements, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS) and adverse event reporting.

Exploratory:

- For Parts A and B, the exploratory objectives are to compare the effect of 7 days administration of SAGE-217 Capsules to placebo on:
  - Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring), as assessed by the Empatica E4 Wristband. Tremor oscillation, as assessed by multi-dimensional accelerometer measurements (ie, raw accelerometer values) using the Empatica E4 Wristband.
  - Quality of life (QOL), as assessed by TETRAS activities of daily living (ADL), Quality of Life in Essential Tremor Questionnaire (QUEST), and video recording assessment of subjects performing three everyday tasks (drinking a glass of water, fastening a button, and one additional task that the subject experiences difficulty with on a daily basis).

  The above exploratory endpoints may also be assessed for SAGE-217 Oral Solution if sufficient data are available.
- For Part C, the exploratory objectives are to assess the effect of 14 days administration of SAGE-217 Capsules on:
  - Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring), as assessed by the Empatica E4 Wristband. Tremor oscillation, as assessed by multi-dimensional accelerometer measurements (ie, raw accelerometer values) using the Empatica E4 Wristband.
  - Quality of life (QOL), as assessed by TETRAS activities of daily living (ADL), Quality of Life in Essential Tremor Questionnaire (QUEST), and video recording assessment of subjects performing three everyday tasks (drinking a glass of water, fastening a button, and one additional task that the subject experiences difficulty with on a daily basis).

In addition, in Parts A, B, and C, plasma concentrations of SAGE-217 and SAGE-217 metabolites may be measured. Pharmacokinetic parameters, such as area under the concentration-time curve from time zero to last time point (AUC_{0-t}), 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}), and terminal half-life ($t_{½}$), will be derived, where appropriate. PK/pharmacodynamic (PD) modelling assessment of the relationship between plasma exposure of SAGE-217 and change from baseline in Kinesia scores may be assessed.

Number of subjects (planned):

Parts A and B are closed to enrollment. For Part C, approximately 15 subjects will be enrolled to ensure at least 10 subjects complete the study (through Day 15).

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Subject has signed an informed consent form before any study-specific procedures are performed.
2. Subject must be between 18 and 80 years of age, inclusive.
3. Subject must have a diagnosis of ET, defined as bilateral postural tremor and kinetic tremor, involving hands and forearms, that is visible and persistent and the duration is >5 years prior to screening.
4. Subject must have bilateral TETRAS scores of at least two on each side (left and right) for kinetic tremor and at least two on each side (left and right) for either wing beating or forward outstretched postural tremor.
5. Subject must be willing to discontinue medications taken for the treatment of ET, alcohol, nicotine, and caffeine through Day 21 of the study.
6. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests.
7. Intentionally blank (criteria removed in Amendment 4, Version 5)
8. Intentionally blank (criteria removed in Amendment 4, Version 5)
9. Intentionally blank (criteria removed in Amendment 4, Version 5)
10. 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 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

Exclusion criteria:

1. Subject has presence of abnormal neurological signs other than tremor or Froment's sign.
2. Subject has presence of known causes of enhanced physiological tremor.
3. Subject has concurrent or recent exposure (14 days prior to Day -1 visit) to tremorogenic drugs, as defined in Appendix 1, or the presence of a drug withdrawal state.
4. Subject has had direct or indirect trauma to the nervous system within 3 months before the onset of tremor.
5. Subject has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.).
6. Subject has convincing evidence of sudden tremor onset or evidence of stepwise deterioration of tremor.
7. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.
8. Intentionally blank (criteria removed in Amendment 4, Version 5)

9. Subject has a history, presence, and/or current evidence of serologic positive results for hepatitis B surface antigen, hepatitis C antibodies, or human immunodeficiency virus 1 or 2 antibodies.
10. Subject has hypothyroidism. Stable thyroid replacement is acceptable.
11. Subject has used alcohol, caffeine, or nicotine within 3 days prior to the Day -1 visit.
12. Subject has a known allergy to SAGE-217, or any capsule excipient.
13. Subject has exposure to another investigational medication or device within the prior 30 days.
14. Subject has a history of suicidal behavior within 2 years or answers "YES" to questions 3, 4, or 5 on the C-SSRS at the Screening visit or on Day -1 or is currently at risk of suicide in the opinion of the Investigator.
15. Subject has donated one or more units (1 unit = 450 mL) of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing.
16. Subject is unwilling or unable to comply with study procedures.
17. Use of any known strong inhibitors and/or inducers of cytochrome P450 (CYP) 3A4, as defined in Appendix 2, within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.
18. Intentionally blank (criteria removed in Amendment 4, Version 5)
19. Subject has concurrent or recent exposure (14 days prior to the Day -1 visit) to sedative/hypnotic (eg, opioids) drugs.
20. Intentionally blank (criteria removed in Amendment 4, Version 5)

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 and administered as an approximate 40 mL solution with a 10 mg, 20 mg, or 30 mg dose given once daily in the morning with food.

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.

See the Pharmacy Manual for information regarding which capsules are to be administered for each dose.

Reference therapy, dosage and mode of administration:

Placebo is available as a solution of 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection and administered as an approximate 40 mL solution given once daily in the morning with food in Part B. Matched placebo capsules containing only the above-listed capsule excipients will be provided. Subjects randomized to placebo treatment will be administered 2 placebo capsules per day.

Duration of treatment:

Screening Duration: up to 28 days; Treatment Period: 14 days; Follow-up: 14 days

Planned Study Duration per Subject: up to 56 days

Criteria for evaluation:

Efficacy:

Tremor severity will be measured by accelerometer-based Kinesia and clinician-rated TETRAS Performance Subscale scores. The following measures will be exploratory measures. Quality-of-life will be evaluated using the TETRAS ADL, QUEST, and video recording of subjects performing three everyday tasks. Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) and tremor oscillation will be assessed by the Empatica E4 Wristband.

Pharmacokinetics:

Plasma will be collected to assay for concentrations of SAGE-217 and may be assayed for SAGE-217 metabolites, if deemed necessary. The following PK parameters will be derived from the plasma concentrations (where evaluable): $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, and $t_{½}$.

Safety and Tolerability:

Safety and tolerability of study drug will be evaluated by vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, and adverse event reporting. The Bond-Lader Mood Rating Scale and a DEQ-5 will be used to assess mood and perception of drug effects, respectively.

Statistical methods:

Study Populations

The safety population is defined as all subjects who are administered at least one dose of study drug.

The efficacy population will consist of all subjects in the safety population who complete at least one dose and have at least one post-dose efficacy evaluation (Kinesia assessment).

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

Efficacy Analysis

Analyses will be done separately for each part.

Efficacy data (including change from randomization or baseline values for accelerometer-derived Kinesia and clinician-rated TETRAS scores) will be summarized using appropriate descriptive statistics and listed by subject.

The change from randomization or baseline in the Kinesia kinetic tremor combined score (ie, the sum of Kinesia kinetic tremor scores from both sides of the body) at Day 14 or 15 will be summarized by treatment. Additionally, the change from randomization or baseline in the Kinesia upper limb total score and individual item scores at Day 14 or 15 will be summarized by treatment.

The change from randomization or baseline in TETRAS upper limb total score, individual TETRAS Performance Subscale upper limb item scores, and other TETRAS Performance Subscale scores at Day 14 or 15 will also be summarized by treatment.

Pharmacokinetic Analysis

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics and listed by subject. Wherever necessary and appropriate, PK parameters will be dose-adjusted to account for individual differences in dose.

Safety Analysis

Adverse events will be coded using Medical Dictionary for Regulatory Activities™. The overall incidence of adverse events will be displayed by System Organ Class, preferred term, and dose group. Incidence of adverse events will also be presented by maximum severity and relationship to study drug. Data from vital signs, clinical laboratory measures, ECG, and C-SSRS will be summarized using descriptive statistics by dose group, where applicable. Continuous endpoints will be summarized with 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 the same summary 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.

Sample Size

Parts A and B are closed to enrollment. Approximately 15 subjects will be enrolled in Part C to ensure 10 subjects complete the study (through Day 15). The sample size for Part C was selected based on clinical and not statistical considerations.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 3: Schedule of Events: Part B (Randomized Withdrawal)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[o] To include those taken throughout the study.

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

Table 4: Schedule of Events: Part C (Open-Label)

Study Procedure	**Study Period / Visit Day**						
	Screening		**Treatment[a]**			**Follow-up**	
	Day -28 to Day -1	**Day -1**	**Day 1**	**Day 8**	**Day 15**	**Day 21±1 day[b]** (Early Termination Visit)	**End of Study Day 28±1 day**
Informed consent	X						
Inclusion/exclusion	X	X					
Demographics	X						
Medical history	X						
Physical examination	X		X	X	X	X	X
Body weight/height	X						
Drug/alcohol screen[c]	X	X		X			
Complete blood count/ serum chemistry[d]	X	X	X	X	X	X	X
Pregnancy test	X (serum)	X (urine)				X (urine)	X (urine)
Urinalysis[d]	X	X	X	X	X	X	X
Hepatitis & HIV screen	X						
Exploratory biochemistry sample[e]	O			O	O	O	
Genetic sample[f]	O					O	
Vital signs[g]	X	X	X	X	X	X	X
12-lead ECG[h]	X	X	X	X	X	X	X
C-SSRS[i]	X	X	X	X	X	X	X
Bond-Lader-VAS[j]			X	X	X	X	
DEQ-5[k]				X	X	X	

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

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

Note: Pre-dose assessments refer to the evening dose only.

[a] An unscheduled visit may be needed if a dose adjustment is deemed necessary by the Investigator at any time during the treatment period in order for the adjusted dose to be dispensed.

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

[c] A urine sample for assessment of selected drugs (sedative/hypnotics [eg, opioids], cotinine, and caffeine) and a breath sample for alcohol screen will be collected at screening, Day -1 and Day 8.

[d] Screening and safety laboratory tests will be performed at screening, Day -1, predose on Day 1, predose on Day 8, on Day 15, and follow-up on Day 21 and Day 28.

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

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

[g] Vital signs (heart rate, respiratory rate, temperature, and supine [for at least 5 minutes prior to the measurement] and standing [for at least 2 to 3 minutes] systolic and diastolic blood pressure) will be performed at screening, Day -1, predose on Day 1 and Day 8, on Day 15, and at follow-up on Day 21 and Day 28.

[h] 12-lead ECGs will be performed at screening, on Day -1, predose on Days 1 and 8, on Day 15, and follow-up on Days 21 and 28.

[i] The C-SSRS will be performed at screening, on Day -1, predose on Days 1 and 8, on Day 15, and follow-up on Days 21 and 28. Baseline/Screening version of C-SSRS should be used on day of screening and Since Last Visit version should be used on all subsequent time points.

[j] The Bond-Lader VAS will be performed predose on Days 1 and 8, on Day 15, and follow-up on Day 21.

[k] The DEQ-5 will be performed predose on Day 8, on Day 15, and follow-up on Day 21.

[l] Kinesia and TETRAS Performance Subscale will be performed at screening and Day -1 (TETRAS Performance Subscale only), and predose on Days 1 and 8, on Day 15, and follow-up on Day 21.

[m] TETRAS ADL Subscale will be performed predose on Days 1 and 8, on Day 15, and follow-up on Day 21.

[n] The Empatica E4 Wristband will be worn at all times (except while bathing) during three 5-day intervals: at the start of the Day -1 visit until the morning of Day 4, at the start of the Day 8 visit until the morning of Day 12, and at the start of the Day 15 visit until the morning of Day 19. The Empatica E4 Wristband will be worn on the wrist that, of the two arms, exhibits more severe tremor symptoms (i.e. tremor-dominant hand), as determined during screening.

[o] Plasma pharmacokinetic samples will be taken predose on Days 1 and 8, and on Day 15.

[p] Study drug will be dispensed at the scheduled clinic visits during the treatment period for outpatient administration daily with food (in the evening on Days 1-3 and in the morning and in the evening on Days 4-14).

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

[r] Videos of subjects performing three everyday tasks (drinking a glass of water, fastening a button, and one additional task that the subject experiences difficulty with on a daily basis) will be taken predose on Day 1 and Day 8, on Day 15, and follow-up on Day 21.

[s] A treatment compliance call will be made within approximately 60 minutes after the scheduled evening dose (between approximately 8:00PM and 9:00PM) on Days 1-14.

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

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 5: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	activities of daily living
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-t}	area under the concentration-time curve from time zero to last time point
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
BMI	body mass index
C_{max}	maximum plasma concentration
CNS	central nervous system
CRF	case report form
CS	clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DEQ-5	Drug Effects Questionnaire
ECG	electrocardiogram
eCRF	electronic CRF
ET	essential tremor
GABA	γ-aminobutyric acid
$GABA_A$	γ-aminobutyric acid-ligand gated chloride channel
$GABA_B$	γ-aminobutyric acid-G protein-coupled
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 Council on Harmonisation
IEC	Independent Ethics Committee

Abbreviation or Specialist Term	Explanation
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCS	not clinically significant
NF	National Formulary
PI	Principal Investigator
PK	pharmacokinetic
QOL	quality of life
QTcF	QT interval calculated using the Fridericia method
QUEST	Quality of Life in Essential Tremor Questionnaire
SRC	Safety Review Committee
SSS	Stanford Sleepiness Scale
TEAEs	treatment-emergent adverse events
TETRAS	TRG Essential Tremor Rating Assessment Scale
$t_{1/2}$	terminal half-life
t_{max}	time to reach maximum concentration
USP	United States Pharmacopeia
VAS	visual analogue score
WHO-DDE	World Health Organization-Drug Dictionary Enhanced
WMA	World Medical Association

5. INTRODUCTION

5.1. Background of Essential Tremor and Unmet Medical Need

Essential tremor (ET) is among the most common neurological diseases, with an overall prevalence of 0.9%. Prevalence increases with age and is estimated to be 4.6% in people over 65 years of age (Louis 2010, Deuschl 2011). Essential tremor is largely a bilateral, symmetrical postural or kinetic tremor involving hands and forearms that is visible and persistent. Additional or isolated tremor of the head or lower limbs may occur, but in the absence of abnormal posturing (Deuschl 1998, Habib-ur-Rehman 2000). The onset of tremor has a bimodal distribution, with onset between 15 to 20 and 50 to 70 years. Over time, tremors can become more pronounced and may prevent eating, drinking, and writing, as well as executing personal hygiene like shaving or applying make-up. Voice tremors can be severe enough to inhibit talking and singing in public.

Several lines of evidence suggest that cerebellar dysfunction through the cerebellothalamocortical pathway plays a key role in ET (McAuley 2000, Pinto 2003, Elble 2009, Schnitzler 2009, Deuschl 2009). Thalamotomy and deep brain stimulation of the ventral intermediate nucleus and of the subthalamic nucleus improve ET (Deuschl 2011, Zappia 2013, Rajput 2014). Microscopic cerebellar pathology has been identified, including gliosis, Purkinje cell loss, and increased torpedoes (swellings) in the Purkinje cell axons (Louis 2007, Axelrad 2008, Shill 2008, Louis 2009). Activation studies with positron emission tomography indicate abnormally increased regional cerebral blood flow in the cerebellum both at rest and when tremor is provoked by unilateral arm extension (Boecker 1994, Wills 1996).

Essential tremor is associated with impaired γ-aminobutyric acid (GABA)ergic function (and consequent hyperactivity) in the cerebellum (Málly 1996, Bucher 1997, Louis 2007, Louis 2008, Paris-Robidas 2012). γ-aminobutyric acid, the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (γ-aminobutyric acid-ligand gated chloride channel [$GABA_A$] and γ-aminobutyric acid-G protein-coupled [$GABA_B$]) on target neurons. γ-aminobutyric acid-gated chloride channel receptors, the major class of inhibitory neurotransmitter receptors in the brain, are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents.

Drugs acting on $GABA_A$ receptors, such as primidone, benzodiazepines, or ethanol decrease tremor amplitude, suggesting that altered GABAergic neurotransmission is involved in ET. Postmortem analysis revealed a 35% reduction of $GABA_A$ receptors and a 22% to 31% reduction of $GABA_B$ receptors in the dentate nucleus of cerebella of ET subjects (Paris-Robidas 2012). Reduced levels of GABA in the cerebrospinal fluid are also reported in ET subjects (Málly 1996). Moreover, toxins such as aflatrem, penitrem A, or harmaline have been proposed to induce tremor in rodents by interacting with GABA receptors (Cavanagh 1998, Miwa 2007), and targeted deletion of the α1 subunit of $GABA_A$ receptor in knockout mice exhibits a 15 to 19 Hz action tremor, similar to ET in humans (Kralic 2005).

Consistent with the role of GABA, the majority of therapeutics for ET act by augmenting GABAergic transmission (Louis 2012, Benito-Leon 2007, Pahapill 1999). First-line treatments

for ET include the anticonvulsant primidone and the β-adrenergic blocker propranolol (Gorman 1986). Like primidone, gabapentin is an anticonvulsant found to be effective in the treatment of ET (O'Brien 1981, Gironell 1999). The oldest treatment for ET is ethanol, which temporarily ameliorates tremor and is frequently used by subjects to self-medicate; however, chronic use of ethanol for tremor management carries the known risks of alcohol dependence and overuse (Pahwa 2003).

These treatments are moderately effective, reducing, though not resolving, tremor amplitudes in about 50% of the subjects (Schmouth 2014). In addition, one out of three patients abandon treatment because of side effects or poor efficacy (Louis 2010), illustrating that with few feasible treatment options and a range of handicaps in daily living makes ET an area of high unmet medical need.

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 ET. Unlike benzodiazepines that are selective for the γ-subunit-containing subset of $GABA_A$ 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 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 as well as 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 which 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, and essential tremor cohorts from Study 217-CLP-101 and the multiple-ascending dose and drug-drug interaction (DDI) 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.

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 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

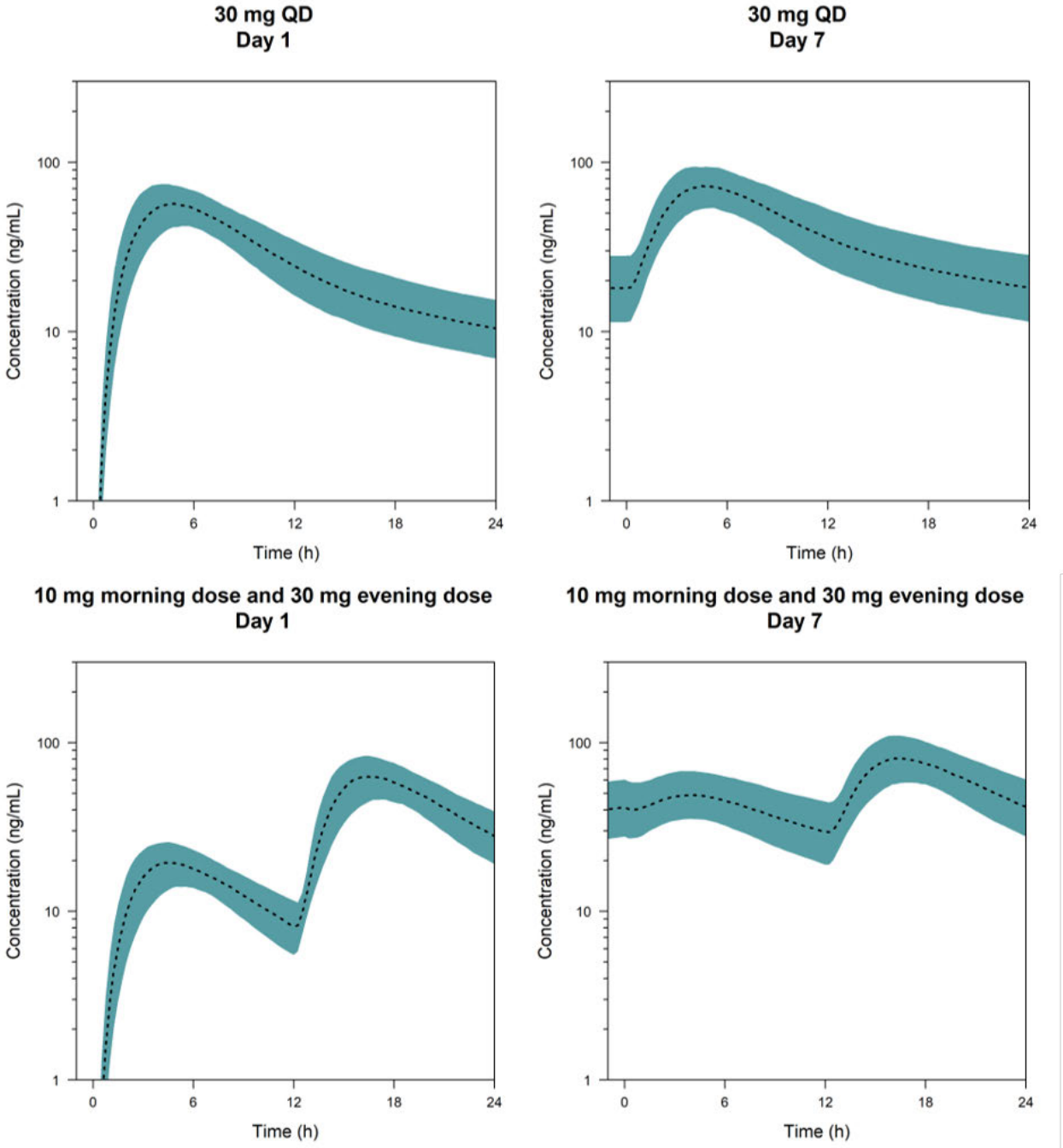
reported in either study. In addition, none of the observed adverse events resulted in discontinuation of the study drug. At doses planned for further study, the observed sedation was mild, transient, and associated with daily peak exposure. The most common treatment-emergent adverse events were sedation, 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 (AM or PM) or 35 mg (PM) 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.

The present study is the first study of SAGE-217 in ET. Preliminary results of the present study demonstrated continued improvement in TETRAS Upper Limb Score over the course of the 7-day treatment with a 30 mg SAGE-217 dose administered each morning. While general improvement was observed, there were two apparent opportunities to optimize the therapeutic utility of SAGE-217 in ETD patients. First, sedation events coincided near the time that SAGE-217 reaches maximal concentrations in plasma. Accordingly, the dose will be administered in the evening in Part C to minimize the impact of sedation. Second, an apparent diminution of TETRAS response was observed at the end of the dosing interval; therefore, in Part C, an additional 10 mg dose will be given in the morning with the intention of elevating plasma concentrations of SAGE-217 to levels associated with beneficial effects, but where sedation is unlikely.

The divided dose regimen will prolong plasma concentrations of SAGE-217, and will increase the C_{max} by approximately 11% at steady-state compared to dosing once per day. Model predictions are dose-proportional and, as such, the 24-hour AUC is expected to increase by 1.33-fold based on the increase in total daily dose from 30 to 40 mg in Part C. Figure 1 compares PK profiles of the dose regimen used in Parts A and B and the proposed 30+10mg regimen in Part C.

Figure 1. Simulated Concentration-Time Curves for SAGE-217 Capsules with Daily and Twice Daily Dosing



QD = once daily
NOTE: Simulations represent the median and 10th to 90th percentiles of the expected plasma concentrations for the regimens as indicated on Day 1 and at steady-state.

5.4. Potential Risks and Benefits

Protocol 217-ETD-201 is the first clinical study of SAGE-217 in ET evaluating the efficacy of this product. 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. Many compounds that target the $GABA_A$ receptors exhibit clinical efficacy in ET, validating this receptor as a therapeutic target. Given the promising SAGE-547 clinical data 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 that have been identified to date, an intra-patient dose-escalation design has been chosen to permit titration of treatment effect vs tolerability (adverse events), specifically sedation. Given the high medical need and potential for benefit in ET, there is a favorable benefit-risk evaluation to investigate SAGE-217 in ET.

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 and generally dissipated by 8 hours. The clinical portion of this study has recently completed; the final report is in progress.

In conclusion, selection criteria for the proposed study take into account the potential safety risks. 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. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Efficacy Objective

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

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

6.2. Secondary Efficacy Objectives

- For Parts A and B, the secondary efficacy objectives are to compare the effect of 7 days administration of SAGE-217 Capsules to placebo on the following endpoints:
  - Tremor severity as assessed by the change from randomization (Day 8) in the Kinesia upper limb total score (ie, the sum of accelerometer-based Kinesia forward outstretched postural tremor, lateral “wing beating” postural tremor, and kinetic tremor item scores from both sides of the body) and individual item scores at Day 14.
  - Tremor severity as measured by the change from randomization (Day 8) in TRG Essential Tremor Rating Assessment Scale (TETRAS) upper limb total score (ie, the sum of TETRAS Performance Subscale item 4 scores [4a, 4b, and 4c] from both sides of the body) and individual TETRAS Performance Subscale upper limb item scores at Day 14.
  - Tremor severity as assessed by the change from randomization (Day 8) in other TETRAS Performance Subscale scores measured at Day 14.

The above endpoints may also be assessed for SAGE-217 Oral Solution if sufficient data are available.

- For Part C, the secondary objectives are to assess the effect of 14 days administration of SAGE-217 Capsules on the following endpoints:
  - Tremor severity, as assessed by the change from baseline (Day 1) in the Kinesia upper limb individual item scores at Day 15.
  - Tremor severity, as measured by the change from baseline (Day 1) in the TETRAS upper limb total score (ie, the sum of TETRAS Performance Subscale item 4 scores [4a, 4b, and 4c] from both sides of the body) and individual TETRAS Performance Subscale upper limb item scores at Day 15.

- Tremor severity, as assessed by the change from baseline (Day 1) in the total TETRAS Performance subscale score and other TETRAS Performance Subscale scores measured at Day 15.

6.3. Safety Objectives

For Parts A, B, and C, safety and tolerability, as assessed by vital signs measurements, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse event reporting.

6.4. Exploratory Objectives

- For Parts A and B, the exploratory objectives are to compare the effect of 7 days administration of SAGE-217 Capsules to placebo on:
  - Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) as assessed by the Empatica E4 Wristband. Tremor oscillation as assessed by multidimensional accelerometer measurements (ie, raw accelerometer values) using the Empatica E4 Wristband.
  - Quality of life (QOL) as assessed by TETRAS activities of daily living (ADL), Quality of Life in Essential Tremor Questionnaire (QUEST), and video recording assessment of subjects performing three everyday tasks (drinking a glass of water, fastening a button, and one additional task that the subject experiences difficulty with on a daily basis).

The above exploratory endpoints may also be assessed for SAGE-217 Oral Solution if sufficient data are available.

- For Part C, the exploratory objectives are to assess the effect of 14 days administration of SAGE 217 Capsules on:
  - Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring), as assessed by the Empatica E4 Wristband. Tremor oscillation, as assessed by multi-dimensional accelerometer measurements (ie, raw accelerometer values) using the Empatica E4 Wristband.
  - Quality of life (QOL), as assessed by TETRAS activities of daily living (ADL), Quality of Life in Essential Tremor Questionnaire (QUEST), and video recording assessment of subjects performing three everyday tasks (drinking a glass of water, fastening a button, and one additional task that the subject experiences difficulty with on a daily basis).

In addition, in Parts A, B, and C, plasma concentrations of SAGE-217 and SAGE-217 metabolites may be measured. Pharmacokinetic parameters, such as area under the concentration-time curve from time zero to last time point (AUC_{0-t}), 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}), and terminal half-life ($t_{½}$), will be derived,

where appropriate. PK and pharmacodynamic modelling assessment of the relationship between plasma exposure of SAGE-217 and change from baseline in Kinesia scores may be assessed.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

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

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

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

The study will be conducted in three parts:

- Part A: Beginning on Day 1, all subjects will receive open-label SAGE-217 in the morning with food (as outlined in Section 9.2) for 7 days. Subjects will receive SAGE-217 10 mg on Day 1, SAGE-217 20 mg on Day 2, and SAGE-217 30 mg from Day 3 to Day 7, with dose adjustments for severe adverse events judged by the Investigator to be related to study drug (Section 9.3).
- Part B: In order to qualify for Part B of the study, a subject must tolerate a dose of ≥10 mg of SAGE-217, and the subject must have responded to SAGE-217, defined as a 30% reduction from baseline in TETRAS kinetic tremor (item 4c) combined score predose on Day 8. Eligible subjects will be randomized in a 1:1 fashion to receive SAGE-217 or placebo for 7 days beginning on Day 8. All doses of study drug will be administered with food as outlined in Section 9.2. Subjects randomized to SAGE-217 or placebo will receive their maximum dose as determined in Part A in the morning with food.
- Part C: All eligible subjects will start on a 10-mg dose of study drug administered with food in the evening on Day 1, 20 mg with food in the evening on Day 2, and 30 mg with food in the evening on Day 3. Beginning on Day 4 and continuing through Day 14, subjects will receive a 40-mg total daily dose (administered as 10 mg with food in the morning and 30 mg with food in the evening). Study drug will be self-administered by subjects on an outpatient basis for the entire 14-day Treatment Period.

Dose adjustments will only be allowed during the open-label phases of the study (Parts A and C, see Section 9.3 for Dose Adjustment Criteria).

7.2. Blinding and Randomization

The double-blind portion of this study (Part B) is closed to enrollment. Part C is open-label with no control group; therefore, there will be no randomization or blinding.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

It is anticipated that up to 60 subjects will be enrolled at up to 25 study centers. The following inclusion and exclusion criteria will be applied during screening for Part A of the study.

8.1. Subject Inclusion Criteria

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

1. Subject has signed an ICF before any study-specific procedures are performed.
2. Subject must be between 18 and 80 years of age, inclusive.
3. Subject must have a diagnosis of ET, defined as bilateral postural tremor and kinetic tremor, involving hands and forearms, that is visible and persistent and the duration is >5 years prior to screening.
4. Subject must have bilateral TETRAS scores of at least two on each side (left and right) for kinetic tremor and at least two on each side (left and right) for either wing beating or forward outstretched postural tremor.
5. Subject must be willing to discontinue medications taken for the treatment of ET, alcohol, nicotine, and caffeine through Day 21 of the study.
6. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests.
7. Intentionally blank (criteria removed in Amendment 4, Version 5)
8. Intentionally blank (criteria removed in Amendment 4, Version 5)
9. Intentionally blank (criteria removed in Amendment 4, Version 5)
10. 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 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

8.2. Subject Exclusion Criteria

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

1. Subject has presence of abnormal neurological signs other than tremor or Froment's sign.
2. Subject has presence of known causes of enhanced physiological tremor.

3. Subject has or recent exposure (14 days prior to the Day -1 visit) to tremorogenic drugs, as defined in Appendix 1, or the presence of a drug withdrawal state.
4. Subject has had direct or indirect trauma to the nervous system within 3 months before the onset of tremor.
5. Subject has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.).
6. Subject has convincing evidence of sudden tremor onset or evidence of stepwise deterioration of tremor.
7. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.
8. Intentionally blank (criteria removed in Amendment 4, Version 5)
9. Subject has a history, presence, and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C antibodies (anti-HCV), or human immunodeficiency virus (HIV) 1 or 2 antibodies.
10. Subject has hypothyroidism. Stable thyroid replacement is acceptable.
11. Subject has used alcohol, caffeine, or nicotine within 3 days prior to the Day -1 visit.
12. Subject has a known allergy to SAGE-217, or any capsule excipient.
13. Subject has exposure to another investigational medication or device within the prior 30 days.
14. Subject has a history of suicidal behavior within 2 years or answers “YES” to questions 3, 4, or 5 on the C-SSRS at the Screening visit or on Day -1 or is currently at risk of suicide in the opinion of the Investigator.
15. Subject has donated one or more units (1 unit = 450 mL) of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing.
16. Subject is unwilling or unable to comply with study procedures.
17. Use of any known strong inhibitors and/or inducers of CYP3A4, as defined in Appendix 2, within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.
18. Intentionally blank (criteria removed in Amendment 4, Version 5)
19. Subject has concurrent or recent exposure (14 days prior to the Day -1 visit) to sedative/hypnotic (eg, opioids) drugs.
20. Intentionally blank (criteria removed in Amendment 4, Version 5)

8.3. Subject Withdrawal Criteria

If there is an adverse event or medical reason for the withdrawal, the subject should be followed medically until the condition has either resolved itself or is stable. Details of the reason for withdrawal should be recorded in the subject's case report form (CRF).

Subjects who withdraw should, if possible, have a follow-up examination, including a physical examination, the appropriate investigations, vital signs, and clinical laboratory tests, as outlined for the Day 21 visit (Table 4). If the subject cannot return on Day 21 (Early Termination visit), their visit can be scheduled at an alternative time, at the discretion of the Investigator and subject. All details of this follow-up examination should be recorded in the subject's medical source documents.

8.3.1. Study Drug Withdrawal

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 at the lowest dose;
- Occurrence of pregnancy;
- Intake of nonpermitted concomitant medication;
- Subject noncompliance;
- Significant protocol deviation determined in consultation with the Medical Monitor.

If a subject failed 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 who withdraw or are withdrawn from the study will be replaced only if they withdraw prior to dosing. Subjects who are withdrawn from the study, fail to return or are no longer qualified will not be replaced.

8.3.2. 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.

9. TREATMENT OF SUBJECTS

9.1. Number of Subjects

Parts A and B are closed to enrollment. For Part C, approximately 15 subjects will be enrolled to ensure at least 10 subjects complete the study (through Day 15).

9.2. Treatment Assignment

Study drug will be administered in the morning with food during Part A and Part B and with food in the evening on Days 1 through 3 and split into 2 doses (10 mg in the morning and 30 mg in the evening) beginning on Day 4 (through Day 14) in Part C.

9.2.1. Part A

Subjects participating in Part A of the study will take study drug (SAGE-217) in an open-label manner. All subjects will start on a 10-mg dose of study drug administered with food in the morning on Day 1. Subjects will receive 20 mg with food on Day 2 and 30 mg with food daily on Days 3 to 7. Dose adjustments may be allowed per the criteria in Section 9.3. The dose tolerated for Days 5, 6, and 7 of the open-label dosing period will be determined to be the maximum dose for that subject.

9.2.2. Part B

Subjects participating in the double-blind, placebo-controlled, randomized withdrawal portion of the study (Part B) will be randomized to SAGE-217 or placebo on Day 8. Subjects randomized to SAGE-217 will receive the maximum dose of SAGE-217 from Part A of the study. Following randomization, subjects will receive 7 days of study drug starting on Day 8.

9.2.3. Part C

All eligible subjects will start on a 10-mg dose of study drug administered with food in the evening (8:00pm ±30 min) on Day 1. Subjects will receive 20 mg with food in the evening on Day 2, and 30 mg with food in the evening on Day 3. Beginning on Day 4 and continuing through Day 14, subjects will receive a 40-mg total daily dose (administered as 10 mg with food in the morning [8:00am ±30 min] and 30 mg with food in the evening [8:00pm ±30 min]).

9.3. Dose Adjustment Criteria

Dose adjustments will only be allowed during the open-label phases of the study (Parts A and C). If at any time the dose is not tolerated in Part A, assessed by occurrence of a severe adverse event judged by the investigator to be related to study drug, the dose on the next day will be reduced to the next lowest dose and continued for the remainder of the open-label dosing period (ie, subjects who are unable to tolerate the 30-mg dose will receive a lower dose of 20 mg, and subjects who are unable to tolerate 20 mg will be given a 10-mg dose). The dose tolerated for Days 5, 6, and 7 of the open-label dosing period will be determined to be the maximum dose for that subject. Subjects who require dose adjustments on Days 5, 6, or 7 of Part A will not progress to Part B.

If at any time the dose is not tolerated in Part C, assessed by occurrence of a severe AE or a moderate AE of special interest (sedation, somnolence, dizziness, euphoric mood, confusion, drowsiness, inebriation (feeling drunk), or fatigue) judged by the investigator to be related to study drug, the dose on the next day will be reduced to the next lowest dose and continued for the remainder of the treatment period. Subjects who cannot tolerate the 20-mg dose on Day 2 will be discontinued. Subjects who do not tolerate 30 mg on Day 3 will receive 20 mg for the remainder of the treatment period (10 mg in the morning and 10 mg in the evening). Subjects who do not tolerate 40 mg on Day 4 or any time thereafter will receive 30 mg for the remainder of the treatment period (10 mg in the morning and 20 mg in the evening). If a dose adjustment is deemed necessary by the Investigator at any time during the treatment period, the subject will return to the site for the adjusted dose to be dispensed.

9.4. Prior/Concomitant Medications and Restrictions

9.4.1. 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 9.4.2.

Record the name, start date (if known), indication for use and whether ongoing or stopped of medications/treatments taken within 2 weeks prior to informed consent and throughout 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.

9.4.2. Prohibited Medications

The drug classes listed in Appendix 1 are not permitted in the 14 days prior to the Day -1 visit and for the duration of the study (up to the Day 28 visit). The list provides non-exhaustive examples of each drug class.

Subjects are not permitted to use alcohol, caffeine, or nicotine within 3 days prior to the Day -1 visit through the Day 21 visit.

For subjects who have previously received primidone or topiramate, a 1-week washout period (prior to Day -1) will be used for subjects with past exposures of ≤1 year and a 2-week washout period (prior to Day -1) will be used for subjects with exposures >1 year. For subjects who have previously received propranolol, a 3-day washout period (prior to Day -1) will be used.

9.5. Treatment Compliance

Investigational product will be dispensed by the site. The Investigator(s) or designee will record the time and dose of study drug administration in the source documents. Any reasons for non-compliance will also be documented, including:

- Missed 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.

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 clinical Good Manufacturing Practice [GMP] conditions at [redacted]) and further admixed at the clinical site in preparation for dosing. Placebo oral solution will be matched to SAGE-217 study drug.

Detailed instructions for study drug preparation will be provided in the Pharmacy Manual.

10.1.1.1. Batch Formula for 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 by [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 6.

Table 6: 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 (Kleptose®)	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

10.1.2. SAGE-217 Capsules

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 one or two capsules per dose.

Matched placebo capsules containing only the above-listed capsule excipients will be provided. Subjects randomized to placebo treatment will be administered 2 placebo capsules per day.

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. Study drug (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. Study drug 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 and placebo), the Investigator or designee will inspect the medication 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 must be carefully stored at the temperature specified in the Pharmacy Manual (eg, clinical dosing solutions stored at approximately 2 to 8°C for 10 days or room temperature for up to 24 hours after preparation), safely and separately from other drugs.

SAGE-217 Capsules and matched placebo 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. Administration and Study Drug Accountability

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 which 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.

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

10.4.1. Study Drug Administration

Subjects in Part A will receive a 10-mg dose of study drug administered in the morning on Day 1, 20 mg on Day 2, and 30 mg on Days 3 to 7.

Subjects in Part B will receive randomized study drug in the morning on Days 8 to 14.

In Part C, study drug will be self-administered by subjects on an outpatient basis for the entire 14-day Treatment Period. Study drug will be dispensed by the clinic on Day 1 and Day 8 (7 days of dosing per dispensation). Subjects will administer a 10-mg dose of study drug in the evening on Day 1, 20 mg on Day 2, 30 mg on Day 3, and 40 mg (administered as one 10 mg dose in the morning and one 30 mg dose in the evening on Days 4 through 14).

10.4.2. Study Drug Accountability

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

In Part C, if a dose adjustment is deemed necessary by the Investigator at any time during the treatment period (see Section 9.3 for dose adjustment criteria), the subject will be instructed to return to the site to return any remaining current dose and for the adjusted dose to be dispensed.

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.

10.5. 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 (oral solution only), administration of test article, 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 subject symptom response by a measurement of Kinesia, TETRAS upper limb items, and TETRAS Performance Subscale (items 4, 6, 7, and 8). Quality-of-life assessments include TETRAS ADL, QUEST, and video recording of subjects performing three everyday tasks. Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) and tremor oscillation as assessed by multidimensional accelerometer measurements (ie, raw accelerometer values) will be assessed by the Empatica E4 Wristband. All efficacy assessments will be performed at the scheduled time points as outlined in the Schedule of Events (Table 4).

11.1. Kinesia

In order to measure tremor amplitude, subjects will wear a wireless ring motion sensor (Kinesia, Great Lakes Neuro Technologies). The motion sensor uses three orthogonal accelerometers and three orthogonal gyroscopes to monitor three-dimensional motion. Data are then transmitted from the sensor to a computer using Bluetooth technology. These measures of three-dimensional motion for each maneuver are then converted to Kinesia scores, which have been shown to correlate with corresponding clinician-rated TETRAS scores (Giovanni 2010). Each Kinesia score ranges from 0 to 4; higher scores indicate more severe tremor. The Kinesia assessment is completed in conjunction with the TETRAS Performance Subscale Item 4 assessment.

11.2. TRG Essential Tremor Rating Assessment Scale (TETRAS) Performance Scale

Item #4 (upper limb tremor) of the TETRAS Performance Subscale will be completed using both the Kinesia device and clinician assessment. Testing should be completed within ±10 minutes of the planned questionnaire time points. All three maneuvers in the upper limb assessments (items 4a, 4b, and 4c) will be completed for both arms, first for the RIGHT arm and then for the LEFT. Predose assessments can be done any time within 2 hours prior to the start of administration of study drug. The Day 21 follow-up visit assessments can be done at any time during the visit.

Note that the TETRAS upper limb scores from the test conducted during screening will be used to determine eligibility and must be ≥2 on each side (left and right) for kinetic tremor and ≥2 on each side (left and right) for either wing beating or forward outstretched postural tremor. A copy of the TETRAS is provided in Appendix 3.

11.3. Empatica E4 Wristband

Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) will be assessed by the Empatica E4 Wristband. The Empatica E4 Wristband is a wearable device that captures motion-based activity and sympathetic nervous system arousal. Data from the Empatica E4 Wristband will not be presented in the study report; instead, they will be part of a separate report.

In Part C, the Empatica E4 Wristband will be worn at all times (except while bathing) during the three 5-day intervals outlined in the Schedule of Events (Table 4). The Empatica E4 Wristband

will be worn on the wrist that, of the two arms, exhibits more severe tremor symptoms (i.e. tremor-dominant hand), as determined during screening.

11.4. Quality of Life in Essential Tremor Questionnaire (QUEST)

The QUEST is a brief, 30-item, ET-specific QOL scale in which subjects rate the extent to which tremor impacts a function or state, tremor severity in various body parts, perceived health, and overall QOL (Tröster 2005). A copy of the QUEST is provided in Appendix 4.

11.5. Video Recording

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

12. PHARMACOKINETICS

12.1. Blood Sample Collection

For plasma sample collection, 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 CRF 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. At sites where a -70°C to -80°C freezer is not available, plasma samples may be stored at -15°C to -30°C prior to being transported for bioanalysis. 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 SAGE-217 will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory.

13. ASSESSMENT OF SAFETY

13.1. Safety and Tolerability Parameters

Safety and tolerability of study drug will be evaluated by vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, and adverse event reporting. The Bond-Lader Mood Rating Scale and a DEQ-5 will be used to assess mood and perception of drug effects, respectively.

13.1.1. Demographic/Medical History

Age, gender, race, and ethnic origin will be recorded at the Screening visit. A full medical history including medication history will be recorded at the Screening visit.

13.1.2. Vital Signs

Vital signs comprise heart rate, respiratory rate, temperature, and supine (supine for at least 5 minutes prior to the measurement) and standing (for at least 2 to 3 minutes) systolic and diastolic blood pressure. Vital sign assessments will be performed within ±10 minutes of the scheduled times.

13.1.3. Weight and Height

Body weight and height will be measured at the Screening visit.

13.1.4. Physical Examination

A physical examination of all major body systems will be undertaken and recorded at the Screening visit.

13.1.5. Electrocardiogram (ECG)

A supine (supine for at least 5 minutes prior to the measurement) 12-lead ECG will be performed at the times specified below and the standard intervals recorded as well as any abnormalities. All ECG results will be interpreted by the Investigator as Normal, Abnormal; not clinically significant (NCS), or Abnormal; clinically significant (CS).

All time points are relative to the time of dosing. ECGs will be performed within ±10 minutes of the predose and 1- and 8-hour time points.

13.1.6. Laboratory Assessments

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 13.2.1, and recorded in the eCRF.

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 4).

13.1.6.1. Hematology

Hematology tests will include complete blood count, 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, AST, and ALT, total protein, and albumin.

Thyroid-stimulating hormone, thyroxine (T4), and triiodothyronine (T3) will be performed at screening to confirm subject eligibility.

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. Drugs Screen and Alcohol Test

A urine sample for assessment of selected drugs (sedative/hypnotics [eg, opioids], cotinine, and caffeine) and a breath sample for alcohol screen will be collected at screening and on Day -1. Results may be obtained through subject history. Subjects who use concomitant sedative/hypnotics will be excluded from the study. Use of alcohol, caffeine, or cotinine is not allowed through Day 21.

13.1.6.5. Virus Serology

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

13.1.6.6. Pregnancy Test

Females of child-bearing potential will be tested for pregnancy by serum or urine pregnancy test as outlined in the Schedule of Events (Table 4).

13.1.6.7. Exploratory Biochemistry

Optional blood samples will be collected at screening and on Days 3 and 7 and may be analyzed for exploratory biochemistry, where consent is given. Future research may suggest other biochemical markers as candidates for influencing not only response to SAGE-217 but also susceptibility to disorders for which SAGE-217 may be evaluated. Thus, the biochemical research may involve study of additional unnamed biochemical biomarkers, but only as related to disease susceptibility and drug action.

13.1.6.8. Genetic Testing

Where consent is given, an optional genetic sample for biomarker testing will be collected at the Screening visit.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (ie, distribution, safety, tolerability, and efficacy) to SAGE-217. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (eg, cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of SAGE-217 (eg, AKR1C4 [3α-hydroxysteroid dehydrogenase]), genes associated with the γ-aminobutyric acid (GABA) receptor (eg, GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3), and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-217 but also susceptibility to disorders for which SAGE-217 may be evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

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 at screening (lifetime history and past 24 months) and the "Since Last Visit" version should be used on all subsequent time points. The C-SSRS is provided in Appendix 5.

13.1.8. Bond-Lader VAS Mood Scale

Mood will be assessed using the Bond-Lader Mood Rating Scale (Bond 1974). This is a 16-part self-administered questionnaire that employs a 100-mm VAS to explore different aspects of self-reported mood. The Bond-Lader Mood Rating Scale is provided in Appendix 6.

13.1.9. Drug Effects Questionnaire (DEQ-5)

A DEQ-5 (Morean 2013) will be administered as follows:

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

5. Would you like MORE of the drug you took, right now?

The answers are recorded on a 100-mm VAS, with the answer for each being "Not at all" and "Extremely" at the extremes. There will be options to record "Not applicable" for questions 3 and 4 if no drug effects are felt and for question 5 prior to administration of study medication. The DEQ-5 is provided in Appendix 7.

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 causally 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.

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, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics or designee for

the duration of the study (from the signing of the ICF through the Day 28 visit [or early termination]).

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. 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, 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.

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. 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.
Probably 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. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

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 through the Day 28 visit (or early termination). 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)

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 28 visit (14 days following the last dose of study drug) or early termination. 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 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.

The efficacy population will consist of all subjects in the safety population who complete at least one dose and have at least one post-dose efficacy evaluation (Kinesia assessment).

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

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, race, and ethnicity, and baseline characteristics, such as height, weight, and BMI, will be summarized.

Categorical summaries, such as race and ethnicity, 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, drug, 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. Primary Efficacy Endpoint

Analysis will be done separately for each study part.

For Parts A and B, the change from baseline or randomizationin the accelerometer-based Kinesia kinetic tremor combined score (ie, the sum of Kinesia kinetic tremor scores from both sides of the body) at Day 14 will be summarized. In Part C, the change from baseline in the accelerometer-based Kinesia™ upper limb tremor combined score (ie, the sum of accelerometer-based Kinesia forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores from both sides of the body) at Day 15 will be summarized.

Change from randomization or baseline to each assessment in Kinesia kinetic tremor combined score will be analyzed using a mixed effects repeated measures model, including center, treatment, randomization Kinesia kinetic tremor combined score, assessment time point, and time point-by-treatment. All explanatory variables will be treated as fixed effects.

14.5. Secondary Efficacy Endpoints

Analysis will be done separately for each study part.

The change from randomization or baseline in the Kinesia upper limb total and individual item scores, TETRAS upper limb total and individual upper limb item scores, and other TETRAS Performance Subscale scores at Day 14 or 15 will be summarized by treatment group.

A mixed effects repeated measures model similar to those described in Section 14.4 will be used for the analysis of change from randomization or baseline in the following: Kinesia upper limb total score, Kinesia individual item scores, TETRAS upper limb total score, and TETRAS individual upper limb item scores.

14.6. Exploratory Efficacy Endpoints

Analysis will be done separately for each study part.

The change from randomization (predose on Day 8) in TETRAS ADL scores at Day 14 or 15 will be summarized.

QUEST data will be listed by subject, study day, and time point.

14.7. Safety and Tolerability Analyses

Data from vital signs, clinical laboratory measures, ECG, and C-SSRS will be summarized using descriptive statistics by group and time point, where applicable. Continuous endpoints will be summarized with 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.

14.7.1. 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 and relationship to study drug (see Section 13.3).

TEAEs 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 signing of the ICF) through the Day 28 visit will be listed.

14.7.2. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from randomization or baseline in vital signs will be evaluated by time point.

14.7.3. Physical Examinations

Screening physical examinations will be documented as done/not done; these results will be listed by subject. Any clinically significant physical examination findings will be recorded as medical history.

14.7.4. 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.

14.7.5. Clinical Laboratory Evaluations

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline or randomization in clinical laboratory measures will be evaluated.

14.7.6. 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.

14.7.7. Bond-Lader VAS Mood Scale

Mood data collected on the Bond-Lader VAS mood scale will be listed by subject, study day, and time point. The scores and change from Day 1 will be summarized by study day and time point.

14.7.8. Drug Effects Questionnaire (DEQ-5)

Results from DEQ-5 will be listed by subject, study day, and time point. The result for each question and change from Day 1 will be summarized by study day and time point.

14.7.9. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and will be coded using World Health Organization-Drug Dictionary Enhanced (WHO-DDE) version 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 within 2 weeks prior to the signing of the ICF. 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 part in which they are being taken. If a concomitant medication assigned to a 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.

14.8. Pharmacokinetic Analysis

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics. Time to reach maximum concentration (t_{max}) will be summarized using 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.

Pharmacokinetic and pharmacodynamic modelling assessment of the relationship between plasma exposure of SAGE-217 and change from baseline in Kinesia scores may be assessed.

14.9. Determination of Sample Size

Parts A and B are closed to enrollment. Approximately 15 subjects will be enrolled in Part C to ensure 10 subjects complete the study (through Day 15). The sample size for Part C was selected based on clinical and not statistical considerations.

14.10. 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 subject into the study, a representative of Sage Therapeutics or designee will visit the investigational study site to:

- Determine the adequacy of the facilities; and
- 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 CRFs, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject'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 subject (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 CRFs 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 subject 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 CRFs.

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 CRFs 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 trial 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.

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21. APPENDICES

Copies of scales and questionnaires included in Appendix 3 through Appendix 7 are for reference only; the rating scales and questionnaires are to be used for actual subject assessment per the Schedule of Events.

APPENDIX 1. 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 28 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 2. STRONG INHIBITORS AND INDUCERS OF CYP3A4

The following known strong inhibitors/inducers of CYP3A4 are not permitted within the 14 days or 5 half-lives (whichever is longer) prior to receiving the first dose of study drug:

Strong inhibitors of CYP3A4:	**Strong inducers of CYP3A4:**
Indinavir	Carbamazepine
Nelfinavir	Efavirenz
Ritonavir	Nevirapine
Clarithromycin	Phenobarbital
Telithromycin	Phenytoin
Iitraconazole	Pioglitazone
Ketoconazole	Rifabutin
Nefazodone	Rifampin
Erythromycin	Troglitazone
Cobistat	Enzalutamide
	Mitotane

APPENDIX 3. TRG ESSENTIAL TREMOR RATING ASSESSMENT SCALE (TETRAS)

TRG ESSENTIAL TREMOR RATING ASSESSMENT SCALE (TETRAS©) V 3.3

Activities of Daily Living Subscale

Rate tremor's impact on activities of daily living (0 - 4 scoring).

1. Speaking
0 = Normal.
1 = Slight voice tremulousness, only when "nervous".
2 = Mild voice tremor. All words easily understood.
3 = Moderate voice tremor. Some words difficult to understand.
4 = Severe voice tremor. Most words difficult to understand.

2. Feeding with a spoon
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with feeding with a spoon.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task, such as using two hands or leaning over.
4 = Severely abnormal. Cannot feed with a spoon.

3. Drinking from a glass
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with drinking from a glass.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.

4. Hygiene
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with hygiene.
2 = Mildly abnormal. Some difficulty but can complete task.
3 = Moderately abnormal. Unable to do most fine tasks such as putting on lipstick or shaving unless changes strategy, such as using two hands or using the less affected hand.
4 = Severely abnormal. Cannot complete hygiene activities independently.

5. Dressing
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with dressing.
2 = Mildly abnormal. Able to do everything but has difficulty due to tremor.
3 = Moderately abnormal. Unable to dress without using strategies such as using Velcro, buttoning shirt before putting it on, andusing shoes with laces.
4 = Severely abnormal. Cannot dress independently.

6. Pouring
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with pouring.
2 = Mildly abnormal. Must be very careful to avoid spilling but may spill occasionally.
3 = Moderately abnormal. Must use two hands or uses other strategies to avoid spilling.
4 = Severely abnormal. Cannot pour.

7. Carrying food trays, plates or similar items
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with carrying food trays, plates or similar items.
2 = Mildly abnormal. Must be very careful to avoid spilling items on food tray.
3 = Moderately abnormal. Uses strategies such as holding tightly against body to carry.
4 = Severely abnormal. Cannot carry food trays or similar items.

8. Using Keys
0 = Normal
1 = Slightly abnormal. Tremor is present but can insert key with one hand without difficulty.
2 = Mildly abnormal. Commonly misses target but still routinely puts key in lock with one hand.
3 = Moderately abnormal. Needs to use two hands or other strategies to put key in lock.
4 = Severely abnormal. Cannot put key in lock.

9. Writing
0 = Normal
1 = Slightly abnormal. Tremor present but does not interfere with writing.
2 = Mildly abnormal. Difficulty writing due to the tremor
3 = Moderately abnormal. Cannot write without using strategies such as holding the writing hand with the other hand, holding pen differently or using large pen.
4 = Severely abnormal. Cannot write.

10. Working: If patient is retired, ask as if they were still working. If the patient is a housewife, ask the question as it relates to housework:
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not affect performance at work or at home.
2 = Mildly abnormal. Tremor interferes with work; able to do everything, but with errors.
3 = Moderately abnormal. Unable to continue working without using strategies such as changing jobs or using special equipment.
4 = Severely abnormal. Cannot perform any job or household work.

11. Overall disability with the most affected task (Name task, e.g. using computer mouse, writing, etc)

Task _____

0 = Normal.
1 = Slightly abnormal. Tremor present but does not affect task.
2 = Mildly abnormal. Tremor interferes with task, but patient is still able to perform task.
3 = Moderately abnormal. Can do task but must use strategies.
4 = Severely abnormal. Cannot do the task.

12. Social Impact

0 = None
1 = Aware of tremor, but it does not affect lifestyle or professional life.
2 = Feels embarrassed by tremor in some social situations or professional meetings.
3 = Avoids participating in some social situations or professional meetings because of tremor.
4 = Avoids participating in most social situations or professional meetings because of tremor.

Performance Subscale

Instructions

Scoring is 0 – 4. For most items, the scores are defined only by whole numbers, but 0.5 increments may be used if you believe the rating is between two whole number ratings and cannot be reconciled to a whole number. Each 0.5 increment in rating is specifically defined for the assessment of upper limb postural and kinetic tremor and the dot approximation task (items 4 and 8). All items of the examination, except standing tremor and heel-knee-shin testing, are performed with the patient seated comfortably. For each item, score the highest peak-to-peak amplitude seen at any point during the exam. Instruct patients not to attempt to suppress the tremor, but to let it come out.

1. Head tremor: The head is rotated fully left and then right for 10s each and is then observed for 10s in mid position. Patient then is instructed to gaze fully to the left and then to the right for 10s each with the head in mid position. The nose or chin should be used as the landmark to rate the largest amplitude excursions during the examination.

   0 = no tremor
   1 = slight tremor (< 0.5 cm)
   2 = mild tremor (0.5- < 2.5 cm)
   3 = moderate tremor (2.5-5 cm)
   4 = severe or disfiguring tremor (> 5 cm)

2. Face (including jaw) tremor: Smile, close eyes, open mouth, purse lips. The highest amplitude of the most involved facial anatomy is scored, regardless of whether it occurs during rest or activation. Repetitive blinking or eye fluttering should not be considered as part of facial tremor.

   0 = no tremor
   1 = slight; barely perceptible tremor
   2 = mild; noticeable tremor
   3 = moderate; obvious tremor, present in most voluntary facial contractions
   4 = severe; gross disfiguring tremor

3. Voice tremor: First ask subject to produce an extended "aaah" sound and eee" sound for 5 seconds each. Then assess speech during normal conversation by asking patients "How do you spend your average day?".

   0 = no tremor
   1 = slight: tremor during aaah or eee, but no tremor during speech
   2 = mild: tremor in "aaah" and "eee" and minimal tremor in speech
   3 = moderate: obvious tremor in speech that is fully intelligible
   4 = severe: some words difficult to understand

4. Upper limb tremor: Tremor is assessed during three maneuvers: forward horizontal reach posture, lateral "wing beating" posture, and finger-nose-finger testing. Each upper limb is assessed and scored individually. The forward horizontal posture is held for 5 seconds. The

lateral wing beating posture is held for 20 seconds. The finger-nose-finger movement is executed three times. Amplitude assessment should be based on the maximum displacement of any part of the hand. For example, the amplitude of a pure supination-pronation tremor, pivoting around the wrist would be assessed at either the thumb or fifth digit.

a. Forward outstretched postural tremor: The upper limb is extended directly forward and parallel to the ground. The wrist should be straight, and the fingers extended and abducted so that they do not touch each other.
b. Lateral "wing beating" postural tremor: The arm is extended laterally, parallel to the ground, the elbow is flexed, and the wrist and fingers are extended so that the fingertip of the extended middle finger is positioned in front of the nose. The fingers are abducted so that they do not touch each other. This posture should be held for 20 seconds, one limb at a time.
c. Kinetic tremor: Subjects extend only their index finger. They then touch a set object or the examiners finger located to the full extent of their reach, which is located at the same height (parallel to the ground) and slightly lateral to the midline. Subjects then touch their own nose (or chin if the tremor is severe) and repeat this back and forth three times. Patients should be instructed to touch the tip of their nose or chin and the examiner's finger tip as precisely as possible. Rapid careless movements should be discouraged. Only the greatest tremor amplitude during the finger-nose-finger movement is assessed. This will typically occur at the nose/chin or at the point of full limb extension (target finger).

For all three hand tremor ratings

0 = no tremor
1 = tremor is barely visible (< 0.5 cm)
1.5 = tremor is visible, but less than 1 cm
2 = tremor is 1- < 3 cm amplitude
2.5 = tremor is 3- < 5 cm amplitude
3 = tremor is 5- < 10 cm amplitude
3.5 = tremor is 10- < 20 cm amplitude
4 = tremor is ≥ 20 cm amplitude

5. Lower limb tremor: Raise each lower limb horizontally and parallel to the ground for 5 seconds. Each lower limb is assessed individually. Then perform a standard heel to shin maneuver with each leg, three times, with patient in supine position. The maximum tremor in either maneuver is scored, and only the limb with the largest tremor is scored. Tremor may emerge from any part of the limb, but tremulous displacement of the foot should be scored as follows:

0 = no tremor
1 = slight: barely perceptible (< 0.5 cm)
2 = mild, less than 1 cm at any point
3 = moderate tremor, less than 5 cm at any point
4 = severe tremor, ≥ 5 cm

6. Archimedes spirals: Demonstrate how to draw Archimedes spiral that approximately fills ¼ of an unlined page of standard (letter) paper. The lines of the spiral should be approximately 1.3 cm (0.5 inch) apart. Then ask the subject to copy the spiral. Test and score each hand

separately. Use a ballpoint pen. The pen should be held such that no part of the limb touches the paper or table. Secure the paper on the table in a location that is suitable for the patient's style of drawing. Score the tremor in the spiral, not the movement of the limb.

0 = normal
1 = slight: tremor barely visible.
2 = mild: obvious tremor
3 = moderate: portions of figure not recognizable.
4 = severe: figure not recognizable

7. Handwriting: Have patient write the standard sentence "This is a sample of my best handwriting" using the dominant hand only. Patients must write cursively (i.e., no printing). They cannot hold or stabilize their hand with the other hand. Use a ballpoint pen. Secure the paper on the table in a location that is suitable for the patient's style of writing. Score the tremor in the writing, not the movement of the limb.

0 = normal
1 = slight: untidy due to tremor that is barely visible.
2 = mild: legible, but with considerable tremor.
3 = moderate: some words illegible.
4 = severe: completely illegible

8. Dot approximation task: The examiner makes a dot or X on a piece of paper and instructs the subject to hold the tip of the pen "as close as possible to the dot or center of the X without touching it (ideally approximately 1 mm), for 10 seconds". Each hand is scored separately.

0 = no tremor
1 = tremor is barely visible (< 0.5 cm)
1.5 = tremor is visible, but less than 1 cm
2 = tremor is 1- < 5 cm amplitude
2.5 = tremor is 3- < 5 cm amplitude
3 = tremor is 5- < 10 cm amplitude
3.5 = tremor is 10- < 20 cm amplitude
4 = tremor is ≥ 20 cm amplitude

9. Standing tremor: Subjects are standing, unaided if possible. The knees are 10-20 cm apart and are flexed 10-20°. The arms are down at the subject's side. Tremor is assessed at any point on the legs or trunk.
0 = no tremor
1 = barely perceptible tremor
2 = obvious but mild tremor, does not cause instability
3 = moderate tremor, impairs stability of stance
4 = severe tremor, unable to stand without assistance

Appendix 4. QUALITY OF LIFE IN ESSENTIAL TREMOR QUESTIONNAIRE (QUEST)

Quality of Life in Essential Tremor Questionnaire (QUEST)

Patient's Name: _____ ID: _____ Date: ____/____/____

Gender: ☐ Male ☐ Female Date of Birth: ____/____/____

Heath Status

In general, how would you rate your overall health? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

Overall Quality of Life

Overall, how would you rate your quality of life? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

General Information

In the past month, has your tremor interfered with your sexual satisfaction?	**Y**	**N**
In the past month, have you had side effects from tremor medications?	Y	N
In the past month, have you been satisfied with the tremor control achieved by your medications?	**Y**	**N**

Which most appropriately describes your work status?

- ☐ Never worked
- ☐ Not working, retired because of tremor
- ☐ Not working, retired NOT due to tremor
- ☐ Working full time
- ☐ Working part time

TREMOR SELF ASSESSMENT

For the purposes of this questionnaire, tremor is defined as uncontrollable shaking or quivering of the body part in question.

On a typical day, how many of your waking hours do you have tremor in ANY body part?

Circle: 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Put a mark in the box to rate the severity of your tremor in each of the body parts listed below.

None - no tremor at any time
Mild - mild tremor not causing difficulty in performing any activities
Moderate - tremor causes difficulty in performing **some** activities
Marked - tremor causes difficulty in performing **most** or **all** activities
Severe - tremor **prevents** performing some activities

		None	Mild	Moderate	Marked	Severe
1.	**Head**	☐	☐	☐	☐	☐
2.	Voice	☐	☐	☐	☐	☐
3.	**Right arm/hand**	☐	☐	☐	☐	☐
4.	Left arm/hand	☐	☐	☐	☐	☐
5.	**Right leg/foot**	☐	☐	☐	☐	☐
6.	Left leg/foot	☐	☐	☐	☐	☐

continued on next page

For each question below, please mark the box which best describes your current situation.

For example: N R ~~S~~ F A

N = Never/No
R = Rarely
S = Sometimes
F = Frequently
A = Always/Yes
NA = Not Applicable

1.	My tremor interferes with my ability to communicate with others.		N R S F A
2.	My tremor interferes with my ability to maintain conversations with others.		N R S F A
3.	It is difficult for others to understand my speech because of my tremor.		N R S F A
4.	My tremor interferes with my job or profession.	NA	N R S F A
5.	I have had to change jobs because of my tremor.	NA	N R S F A
6.	I had to retire or take early retirement because of my tremor.		N A
7.	I am only working part time because of my tremor.	NA	N A
8.	I have had to use special aids or accommodations in order to continue my job due to my tremor.	NA	N R S F A
9.	My tremor has led to financial problems or concerns.		N R S F A
10.	I have lost interest in my hobbies because of my tremor.		N R S F A
11.	I have quit some of my hobbies because of my tremor.		N A
12.	I have had to change or develop new hobbies because of my tremor.		N A
13.	My tremor interferes with my ability to write (for example, writing letters, completing forms).		N R S F A
14.	My tremor interferes with my ability to use a typewriter or computer.	NA	N R S F A
15.	My tremor interferes with my ability to use the telephone (for example, dialing, holding the phone).		N R S F A
16.	My tremor interferes with my ability to fix small things around the house (for example, change light bulbs, minor plumbing, fixing household appliances, fixing broken items).		N R S F A
17.	My tremor interferes with dressing (for example, buttoning, zipping, tying shoes).		N R S F A
18.	My tremor interferes with brushing or flossing my teeth.		N R S F A
19.	My tremor interferes with eating (for example, bringing food to mouth, spilling).		N R S F A
20.	My tremor interferes with drinking liquids (for example, bringing to mouth, spilling, pouring).		N R S F A
21.	My tremor interferes with reading or holding reading material.		N R S F A
22.	My tremor interferes with my relationships with others (for example, my family, friends, coworkers).		N R S F A
23.	My tremor makes me feel negative about myself.		N R S F A
24.	I am embarrassed about my tremor.		N R S F A
25.	I am depressed because of my tremor.		N R S F A
26.	I feel isolated or lonely because of my tremor.		N R S F A
27.	I worry about the future due to my tremor.		N R S F A
28.	I am nervous or anxious.		N R S F A
29.	I use alcohol more frequently than I would like to because of my tremor.		N R S F A
30.	I have difficulty concentrating because of my tremor.		N R S F A

THANK YOU!

APPENDIX 5. COLUMBIA – SUICIDE SEVERITY RATING SCALE (C-SSRS)

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 24 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 24 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)

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime	Past 24 Months
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@nyspi.columbia.edu

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USorf.doc

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USorl.doc

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	___

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 ☐
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 6. BOND-LADER VAS (MOOD RATING SCALE)

1. Please rate the way you feel in terms of the dimensions given below.
2. Regard the line as representing the full range of each dimension.
3. Rate your feelings as they are at the moment.
4. Mark clearly and perpendicularly across each line.

Alert	_____	**Drowsy**
Calm	_____	**Excited**
Strong	_____	**Feeble**
Muzzy	_____	**Clear-headed**
Well-coordinated	_____	**Clumsy**
Lethargic	_____	**Energetic**
Contented	_____	**Discontented**
Troubled	_____	**Tranquil**
Mentally Slow	_____	**Quick-witted**
Tense	_____	**Relaxed**
Attentive	_____	**Dreamy**
Incompetent	_____	**Proficient**
Happy	_____	**Sad**
Antagonistic	_____	**Amicable**
Interested	_____	**Bored**
Withdrawn	_____	**Gregarious**

APPENDIX 7. DRUG EFFECTS QUESTIONNAIRE (DEQ-5)

Instructions: This questionnaire asks about how you are feeling after taking the substance that was given to you. Please draw a mark on the line to show how strongly you are feeling each of the following effects ***right now***. You can mark anywhere on the line, but please draw a vertical line (one that goes straight up and down).

Let's look at an example first.

EXAMPLE: Do you feel dizzy right now?
If you do not feel dizzy, draw a line at NOT AT ALL. If you feel very dizzy, draw a line at EXTREMELY. If you feel somewhere in between, you can draw a mark anywhere along the line between NOT AT ALL and EXTREMELY to indicate how dizzy you are. For example, if you feel a little dizzy, you might draw a line that looks something like the example below.

NOT AT ALL — EXTREMELY

1. Do you FEEL a drug effect right now?

NOT AT ALL — EXTREMELY

2. Are you HIGH right now?

NOT AT ALL — EXTREMELY

3. Do you DISLIKE any of the effects you are feeling right now?

NOT AT ALL — EXTREMELY

4. Do you LIKE any of the effects you are feeling right now?

NOT AT ALL — EXTREMELY

5. Would you like MORE of the drug you took, right now?

NOT AT ALL — EXTREMELY

Protocol Number: 217-ETD-201

A Phase 2A, Double-blind, Placebo-controlled, Randomized Withdrawal Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of SAGE-217 in the Treatment of Subjects with Essential Tremor (ET)

IND Number: 131, 258

Investigational Product	SAGE-217
Clinical Phase	2a
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted], M.S.H.S. [redacted] Phone: [redacted] Email: [redacted]
Medical Monitor	[redacted], M.D., M.P.H. Study Physician Phone: [redacted] Email: [redacted]
Date of Original Protocol	Version 1.0, 19 August 2016
Date of Amendment 1	Version 2.0, 28 October 2016
Date of Amendment 2	Version 3.0, 27 January 2017
Date of Amendment 3	Version 4.0, 28 April 2017

PROTOCOL SIGNATURE PAGE

Protocol Number:	217-ETD-201
Product:	SAGE-217
IND No.:	131,258
Study Phase:	2a
Sponsor:	Sage Therapeutics
Date of Amendment 3:	Version 4.0, 28 April 2017

Sponsor Approval

[redacted] For 20 Apr 2017

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

Sage Therapeutics

[redacted] 28 April 2017

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

[redacted]Therapeutics

[redacted] 28 Apr 2017

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

Sage Therapeutics

[redacted] 28 Apr 2017

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

Sage Therapeutics

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the Clinical Protocol 217-ETD-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
Sponsor Physician	, M.D., M.P.H. Sage Therapeutics	215 First Street, Suite 220 Cambridge, MA 02142 Cell:
Sponsor Signatory	, M.D., Ph.D.	215 First Street, Suite 220 Cambridge, MA 02142 Office: Cell:
Medical Monitor		

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 2a, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of SAGE-217 in the Treatment of Subjects with Essential Tremor (ET)

Study center(s): Up to 25 centers

Phase of development: 2a

Methodology:

This study will assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of SAGE-217. Subjects who consent prior to the approval of Protocol Amendment #3 by the IRB will receive the oral solution formulation for the duration of the study. Subjects who consent after Amendment #3 is approved by the IRB will receive the capsule formulation for the duration of the study.

There are two parts:

Part A: Open-label with morning dosing (7 days).

All subjects will start on a 10-mg dose of study drug administered with food on Day 1. Subjects will receive 20 mg with food on Day 2 and 30 mg with food daily on Days 3 to 7.

Part B: Double-blind, placebo-controlled, randomized withdrawal with morning dosing (7 days).

In order to qualify for Part B of the study, a subject must tolerate a dose of at least 10 mg of SAGE-217, and the subject must have responded to SAGE-217, defined as a 30% reduction from baseline in the TRG Essential Tremor Rating Assessment Scale (TETRAS) kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) predose on Day 8.

Eligible subjects will be randomized in a 1:1 fashion to SAGE-217 or placebo and will receive their maximum dose as determined in Part A in the morning with food. Subjects randomized to the placebo arm will represent randomized withdrawal (withdrawal from treatment they received in Part A).

Methodology:

Dose adjustments will only be allowed during the open-label phase of the study (Part A). If at any time the dose is not tolerated in Part A, assessed by occurrence of a severe adverse event judged by the investigator to be related to study drug, the dose on the next day will be reduced to the next lowest dose and continued for the remainder of the open-label dosing period (ie, subjects who are unable to tolerate the 30-mg dose will receive a lower dose of 20 mg, and subjects who are unable to tolerate 20 mg will be given a 10-mg dose). The dose tolerated for Days 5, 6, and 7 of the open-label dosing period will be determined to be the maximum dose for that subject. Subjects who require dose adjustments on Days 5, 6, or 7 of Part A will not progress to Part B.

Subjects will be exposed to study drug (SAGE-217 or placebo) for up to 14 days and will be followed for an additional 14 days after the administration of the last dose.

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

Objectives:

Primary:

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

Secondary:

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

- Tremor severity, as assessed by the change from randomization (Day 8) in the Kinesia upper limb total score (ie, the sum of accelerometer-based Kinesia forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores from both sides of the body) and individual item scores at Day 14.
- Tremor severity, as measured by the change from randomization (Day 8) in the TETRAS upper limb total score (ie, the sum of TETRAS Performance Subscale item 4 scores [4a, 4b, and 4c] from both sides of the body) and individual TETRAS Performance Subscale upper limb item scores at Day 14.
- Tremor severity, as assessed by the change from randomization (Day 8) in other TETRAS Performance Subscale scores measured at Day 14.
- Safety and tolerability, as assessed by vital signs measurements, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse event reporting.
- Sleepiness, as assessed by the Stanford Sleepiness Scale (SSS).
- Mood, as assessed by the Bond-Lader visual analogue scale (VAS) Mood Scale scores.
- How the subject feels after taking the study drug as assessed by Drug Effects Questionnaire (DEQ-5) ratings.

The above endpoints may also be assessed for SAGE-217 Oral Solution if sufficient data are available.

In addition, plasma concentrations of SAGE-217 and SAGE-217 metabolites may be measured. Pharmacokinetic parameters, such as area under the concentration-time curve from time zero to last time point (AUC_{0-t}), 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}), and terminal half-life ($t_{1/2}$), will be derived, where appropriate.

Exploratory:

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

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

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

The above endpoints may also be assessed for SAGE-217 Oral Solution if sufficient data are available.

Number of subjects (planned):

Approximately 60 subjects will be enrolled in Part A to yield at least 40 randomized subjects for Part B.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Subject has signed an informed consent form before any study-specific procedures are performed.
2. Subject must be between 18 and 75 years of age, inclusive.
3. Subject must have a diagnosis of ET, defined as bilateral postural tremor and kinetic tremor, involving hands and forearms, that is visible and persistent and the duration is >5 years prior to screening.
4. Subject must have bilateral TETRAS scores of at least two on each side (left and right) for kinetic tremor and at least two on each side (left and right) for either wing beating or forward outstretched postural tremor.
5. Subject must be willing to discontinue medications taken for the treatment of ET, alcohol, nicotine, and caffeine through Day 21 of the study.
6. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests.
7. Female subjects must be post-menopausal, permanently sterile (eg, bilateral tubal occlusion, hysterectomy, bilateral oophorectomy), or of childbearing potential with a negative pregnancy test, non- breastfeeding, and using two highly effective methods of birth control prior to screening through completion of the last follow-up visit (as defined in Section 8.1). If a subject discontinues early after receiving a dose of study drug, they 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 are defined as follows: hormonal (ie, established use of oral, implantable, injectable, or transdermal hormonal methods of conception); placement of an intrauterine device; placement of an intrauterine system; and mechanical/barrier method of contraception (ie, condom or occlusive

cap [diaphragm or cervical/vault cap] in conjunction with spermicide [foam, gel, film, cream or suppository]).

8. Male subjects must agree to practice a highly effective method of birth control while on study drug 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.
9. 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. Subject has presence of abnormal neurological signs other than tremor or Froment's sign.
2. Subject has presence of known causes of enhanced physiological tremor.
3. Subject has concurrent or recent exposure (14 days prior to Day -1 visit) to tremorogenic drugs, as defined in Appendix 1, or the presence of a drug withdrawal state.
4. Subject has had direct or indirect trauma to the nervous system within 3 months before the onset of tremor.
5. Subject has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.).
6. Subject has convincing evidence of sudden tremor onset or evidence of stepwise deterioration of tremor.
7. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.
8. Subject has clinically significant abnormal physical examination or 12-lead ECG at the Screening or Day -1 visits. Note: A 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. An ECG may be repeated if initial values obtained exceed the limits specified.
9. Subject has a history, presence, and/or current evidence of serologic positive results for hepatitis B surface antigen, hepatitis C antibodies, or human immunodeficiency virus 1 or 2 antibodies.
10. Subject has hypothyroidism. Stable thyroid replacement is acceptable.
11. Subject has used alcohol, caffeine, or nicotine within 3 days prior to the Day -1 visit.
12. Subject has a known allergy to SAGE-217 or its major excipient hydroxypropyl-β-cyclodextrin (HPβCD).
13. Subject has exposure to another investigational medication or device within the prior 30 days.
14. Subject has a history of suicidal behavior within 2 years or answers "YES" to questions 3, 4, or 5 on the C-SSRS at the Screening visit or on Day -1 or is currently at risk of suicide in the opinion of the Investigator.
15. Subject has donated one or more units (1 unit = 450 mL) of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing.
16. Subject is unwilling or unable to comply with study procedures.
17. Use of any known strong inhibitors and/or inducers of cytochrome P450 (CYP) 3A4, as defined in Appendix 2, within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit

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

18. Subject has obstructed venous access and/or has skin disease, rash, acne, or abrasion at venous access site that may affect the ability to obtain a PK sample (eg, artificial cardiac valve, joint replacement).
19. Subject has concurrent or recent exposure (14 days prior to the Day -1 visit) to sedative/hypnotic (eg, opioids) drugs.
20. Subject has hyperthyroidism at screening (based on thyroid-stimulating hormone, thyroxine [T4], and triiodothyronine [T3]) or clinically significant kidney issues in the opinion of the Investigator.

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 and administered as an approximate 40 mL solution with a 10 mg, 20 mg, or 30 mg dose given once daily in the morning with food.

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.

Reference therapy, dosage and mode of administration:

Placebo is available as a solution of 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection and administered as an approximate 40 mL solution given once daily in the morning with food in Part B. Matched placebo capsules containing only the above-listed capsule excipients will be provided. Subjects randomized to placebo treatment will be administered 2 placebo capsules per day.

Duration of treatment:

Screening Duration: up to 28 days; Treatment Period: 14 days; Follow-up: 14 days

Planned Study Duration per Subject: up to 56 days

Criteria for evaluation:

Efficacy:

Tremor severity will be measured by accelerometer-based Kinesia and clinician-rated TETRAS Performance Subscale scores. Quality-of-life will be evaluated using the TETRAS ADL, QUEST, and video recording of subjects performing three everyday tasks. Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) and tremor oscillation will be assessed by the Empatica Wristband E4.

Pharmacokinetics:

Plasma will be collected to assay for concentrations of SAGE-217 and may be assayed for SAGE-217 metabolites, if deemed necessary. The following PK parameters will be derived from the plasma concentrations (where evaluable): AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{½}$.

Safety and Tolerability:

Safety and tolerability of study drug will be evaluated by vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, SSS, and adverse event reporting. The Bond-Lader Mood Rating Scale and a DEQ-5 will be used to assess mood and perception of drug effects, respectively.

Statistical methods:

Study Populations

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 complete at least one dose in Part B and have at least one post-randomization efficacy evaluation.

The evaluable population will consist of all randomized subjects with at least one post-randomization Kinesia assessment.

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

Efficacy Analysis

Efficacy data (including change from randomization values for accelerometer-derived Kinesia and clinician-rated TETRAS scores) will be summarized using appropriate descriptive statistics and listed by subject.

The change from randomization (Day 8) in the Kinesia kinetic tremor combined score (ie, the sum of Kinesia kinetic tremor scores from both sides of the body) at Day 14 will be summarized by treatment. Additionally, the change from randomization in the Kinesia upper limb total score and individual item scores at Day 14 will be summarized by treatment.

The change from randomization in TETRAS upper limb total score, individual TETRAS Performance Subscale upper limb item scores, and other TETRAS Performance Subscale scores at Day 14 will be summarized by treatment.

Pharmacokinetic Analysis

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics and listed by subject. Wherever necessary and appropriate, PK parameters will be dose-adjusted to account for individual differences in dose.

Safety Analysis

Adverse events will be coded using Medical Dictionary for Regulatory Activities™. The overall incidence of adverse events will be displayed by System Organ Class, preferred term, and dose group. Incidence of adverse events will also be presented by maximum severity and relationship to study drug. Data from vital signs, clinical laboratory measures, ECG, and C-SSRS will be summarized using descriptive statistics by dose group, where applicable. Continuous endpoints will be summarized with 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 the same summary 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.

Sample Size

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 3: Schedule of Events: Part B (Randomized Withdrawal)

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

Table 3: Schedule of Events: Part B (Randomized Withdrawal) (Continued)

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

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

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

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

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

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

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

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

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

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

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

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

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

[l] The Empatica Wristband E4 will be worn during the study visits while in clinic on Days 8, 9, 14, and 21. With the exception of during the TETRAS upper limb assessments, the Empatica Wristband E4 will be worn on the wrist that, of the two arms, exhibits more severe tremor symptoms. During the TETRAS upper limb assessments 3 hours (±30 minutes) postdose on Days 8, 9, and 14 and anytime during the visit on Day 21, the Empatica Wristband E4 will be worn on the wrist corresponding to the side of the body being assessed.

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

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

[c] To include those taken throughout the study.

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

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

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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
ADL	activities of daily living
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-t}	area under the concentration-time curve from time zero to last time point
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
BMI	body mass index
C_{max}	maximum plasma concentration
CNS	central nervous system
CRF	case report form
CS	clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DEQ-5	Drug Effects Questionnaire
ECG	electrocardiogram
eCRF	electronic CRF
ET	essential tremor
GABA	γ-aminobutyric acid
$GABA_A$	γ-aminobutyric acid-ligand gated chloride channel
$GABA_B$	γ-aminobutyric acid-G protein-coupled
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 Council on Harmonisation
IEC	Independent Ethics Committee

Table 4: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCS	not clinically significant
NF	National Formulary
PI	Principal Investigator
PK	pharmacokinetic
QOL	quality of life
QTcF	QT interval calculated using the Fridericia method
QUEST	Quality of Life in Essential Tremor Questionnaire
SRC	Safety Review Committee
SSS	Stanford Sleepiness Scale
TEAEs	treatment-emergent adverse events
TETRAS	TRG Essential Tremor Rating Assessment Scale
$t_{1/2}$	terminal half-life
t_{max}	time to reach maximum concentration
USP	United States Pharmacopeia
VAS	visual analogue score
WHO-DDE	World Health Organization-Drug Dictionary Enhanced
WMA	World Medical Association

5. INTRODUCTION

5.1. Background of Essential Tremor and Unmet Medical Need

Essential tremor (ET) is among the most common neurological diseases, with an overall prevalence of 0.9%. Prevalence increases with age and is estimated to be 4.6% in people over 65 years of age (Louis 2010, Deuschl 2011). Essential tremor is largely a bilateral, symmetrical postural or kinetic tremor involving hands and forearms that is visible and persistent. Additional or isolated tremor of the head or lower limbs may occur, but in the absence of abnormal posturing (Deuschl 1998, Habib-ur-Rehman 2000). The onset of tremor has a bimodal distribution, with onset between 15 to 20 and 50 to 70 years. Over time, tremors can become more pronounced and may prevent eating, drinking, and writing, as well as executing personal hygiene like shaving or applying make-up. Voice tremors can be severe enough to inhibit talking and singing in public.

Several lines of evidence suggest that cerebellar dysfunction through the cerebellothalamocortical pathway plays a key role in ET (McAuley 2000, Pinto 2003, Elble 2009, Schnitzler 2009, Deuschl 2009). Thalamotomy and deep brain stimulation of the ventral intermediate nucleus and of the subthalamic nucleus improve ET (Deuschl 2011, Zappia 2013, Rajput 2014). Microscopic cerebellar pathology has been identified, including gliosis, Purkinje cell loss, and increased torpedoes (swellings) in the Purkinje cell axons (Louis 2007, Axelrad 2008, Shill 2008, Louis 2009). Activation studies with positron emission tomography indicate abnormally increased regional cerebral blood flow in the cerebellum both at rest and when tremor is provoked by unilateral arm extension (Boecker 1994, Wills 1996).

Essential tremor is associated with impaired γ-aminobutyric acid (GABA)ergic function (and consequent hyperactivity) in the cerebellum (Málly 1996, Bucher 1997, Louis 2007, Louis 2008, Paris-Robidas 2012). γ-aminobutyric acid, the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (γ-aminobutyric acid-ligand gated chloride channel [$GABA_A$] and γ-aminobutyric acid-G protein-coupled [$GABA_B$]) on target neurons. γ-aminobutyric acid-gated chloride channel receptors, the major class of inhibitory neurotransmitter receptors in the brain, are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents.

Drugs acting on $GABA_A$ receptors, such as primidone, benzodiazepines, or ethanol decrease tremor amplitude, suggesting that altered GABAergic neurotransmission is involved in ET. Postmortem analysis revealed a 35% reduction of $GABA_A$ receptors and a 22% to 31% reduction of $GABA_B$ receptors in the dentate nucleus of cerebella of ET subjects (Paris-Robidas 2012). Reduced levels of GABA in the cerebrospinal fluid are also reported in ET subjects (Málly 1996). Moreover, toxins such as aflatrem, penitrem A, or harmaline have been proposed to induce tremor in rodents by interacting with GABA receptors (Cavanagh 1998, Miwa 2007), and targeted deletion of the α1 subunit of $GABA_A$ receptor in knockout mice exhibits a 15 to 19 Hz action tremor, similar to ET in humans (Kralic 2005).

Consistent with the role of GABA, the majority of therapeutics for ET act by augmenting GABAergic transmission (Louis 2012, Benito-Leon 2007, Pahapill 1999). First-line treatments

for ET include the anticonvulsant primidone and the β-adrenergic blocker propranolol (Gorman 1986). Like primidone, gabapentin is an anticonvulsant found to be effective in the treatment of ET (O'Brien 1981, Gironell 1999). The oldest treatment for ET is ethanol, which temporarily ameliorates tremor and is frequently used by subjects to self-medicate; however, chronic use of ethanol for tremor management carries the known risks of alcohol dependence and overuse (Pahwa 2003).

These treatments are moderately effective, reducing, though not resolving, tremor amplitudes in about 50% of the subjects (Schmouth 2014). In addition, one out of three patients abandon treatment because of side effects or poor efficacy (Louis 2010), illustrating that with few feasible treatment options and a range of handicaps in daily living makes ET an area of high unmet medical need.

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 ET. Unlike benzodiazepines that are selective for the γ-subunit-containing subset of $GABA_A$ 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 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 as well as 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 which 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, and essential tremor cohorts from Study 217-CLP-101 and the multiple-ascending dose and drug-drug interaction (DDI) 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.

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 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 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 (AM or PM) or 35 mg (PM) 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.

There were no clinical efficacy data of SAGE-217 in ET, since the present study is the first study in this indication.

5.4. Potential Risks and Benefits

Protocol 217-ETD-201 is the first clinical study of SAGE-217 in ET evaluating the efficacy of this product. 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. Many compounds that target the $GABA_A$ receptors exhibit clinical efficacy in ET, validating this receptor as a therapeutic target. Given the promising SAGE-547 clinical data 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 that have been identified to date, an intra-patient dose-escalation design has been chosen to permit titration of treatment effect vs tolerability (adverse events), specifically sedation. Each subject will start with an initial dose of 10 mg to be escalated to 20 mg after a day and then escalated further to 30 mg assuming no tolerability issues. At the end of a 7-day exposure, the maximum dose for the subject will be established as will a protocol specified response. Subjects who are responders and tolerate at least the 10-mg dose for a minimum of 3 days will qualify for the randomization phase (Part B). Given the high medical need and potential for benefit in ET, there is a favorable benefit-risk evaluation to investigate SAGE-217 in ET.

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 and generally dissipated by 8 hours. The clinical portion of this study has recently completed; the final report is in progress.

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. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

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

6.2. Secondary Objectives

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

1. Tremor severity as assessed by the change from randomization (Day 8) in the Kinesia upper limb total score (ie, the sum of accelerometer-based Kinesia forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores from both sides of the body) and individual item scores at Day 14.
2. Tremor severity as measured by the change from randomization (Day 8) in TRG Essential Tremor Rating Assessment Scale (TETRAS) upper limb total score (ie, the sum of TETRAS Performance Subscale item 4 scores [4a, 4b, and 4c] from both sides of the body) and individual TETRAS Performance Subscale upper limb item scores at Day 14.
3. Tremor severity as assessed by the change from randomization (Day 8) in other TETRAS Performance Subscale scores measured at Day 14.
4. Safety and tolerability as assessed by vital signs measurements, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse event reporting.
5. Sleepiness as assessed by the SSS.
6. Mood as assessed by the Bond-Lader visual analogue score (VAS) Mood Scale.
7. How the subject feels after taking the study drug as assessed by Drug Effects Questionnaire (DEQ-5) ratings.

The above endpoints may also be assessed for SAGE-217 Oral Solution if sufficient data are available.

In addition, plasma concentrations of SAGE-217 and SAGE-217 metabolites may be measured. Pharmacokinetic parameters, such as area under the concentration-time curve from time zero to last time point (AUC_{0-t}), 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}), and terminal half-life ($t_{1/2}$), will be derived, where appropriate.

6.3. Exploratory Objectives

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

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

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

The above endpoints may also be assessed for SAGE-217 Oral Solution if sufficient data are available.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

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

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

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

The study will be conducted in two parts:

- Part A: Beginning on Day 1, all subjects will receive open-label SAGE-217 in the morning with food (as outlined in Section 9.2) for 7 days. Subjects will receive SAGE-217 10 mg on Day 1, SAGE-217 20 mg on Day 2, and SAGE-217 30 mg from Day 3 to Day 7, with dose adjustments for severe adverse events judged by the Investigator to be related to study drug (Section 9.3).
- Part B: In order to qualify for Part B of the study, a subject must tolerate a dose of ≥10 mg of SAGE-217, and the subject must have responded to SAGE-217, defined as a 30% reduction from baseline in TETRAS kinetic tremor (item 4c) combined score predose on Day 8. Eligible subjects will be randomized in a 1:1 fashion to receive SAGE-217 or placebo for 7 days beginning on Day 8. All doses of study drug will be administered with food as outlined in Section 9.2. Subjects randomized to SAGE-217 or placebo will receive their maximum dose as determined in Part A in the morning with food.

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

7.2. Blinding and Randomization

Part A is open-label with no control group; therefore, there will be no randomization or blinding.

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

The randomization schedule will be generated prior to the start of the study. The randomization schedule will be generated using SAS V9.2 or later. Only the clinic pharmacist, who is responsible for preparing the study drug for administration, will be given a copy of the randomization schedule. In the event of a medical emergency, the pharmacist may reveal actual study drug contents to the investigator, who should also alert Sage of the emergency (see Section 13.6 for more details related to unblinding). In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and on the electronic case report form (eCRF). If the subject or study center personnel (other than pharmacist) have been unblinded, the subject will be terminated from the study.

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

8. SELECTION AND WITHDRAWAL OF SUBJECTS

It is anticipated that up to 60 subjects will be enrolled at up to 25 study centers. The following inclusion and exclusion criteria will be applied during screening for Part A of the study.

8.1. Subject Inclusion Criteria

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

1. Subject has signed an ICF before any study-specific procedures are performed.
2. Subject must be between 18 and 75 years of age, inclusive.
3. Subject must have a diagnosis of ET, defined as bilateral postural tremor and kinetic tremor, involving hands and forearms, that is visible and persistent and the duration is >5 years prior to screening.
4. Subject must have bilateral TETRAS scores of at least two on each side (left and right) for kinetic tremor and at least two on each side (left and right) for either wing beating or forward outstretched postural tremor.
5. Subject must be willing to discontinue medications taken for the treatment of ET, alcohol, nicotine, and caffeine through Day 21 of the study.
6. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests.
7. Female subjects must be post-menopausal, permanently sterile (eg, bilateral tubal occlusion, hysterectomy, bilateral oophorectomy), or of childbearing potential with a negative pregnancy test, non- breastfeeding, and using two highly effective methods of birth control prior to screening through completion of the last follow-up visit. If a subject discontinues early after receiving a dose of study drug, they 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 are defined as follows: hormonal (ie, established use of oral, implantable, injectable, or transdermal hormonal methods of conception); placement of an intrauterine device; placement of an intrauterine system; and mechanical/barrier method of contraception (ie, condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [foam, gel, film, cream or suppository]).
8. Male subjects must agree to practice a highly effective method of birth control while on study drug 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.
9. 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 the following exclusion criteria will be excluded from the study:

1. Subject has presence of abnormal neurological signs other than tremor or Froment's sign.

2. Subject has presence of known causes of enhanced physiological tremor.
3. Subject has or recent exposure (14 days prior to the Day -1 visit) to tremorogenic drugs, as defined in Appendix 1, or the presence of a drug withdrawal state.
4. Subject has had direct or indirect trauma to the nervous system within 3 months before the onset of tremor.
5. Subject has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.).
6. Subject has convincing evidence of sudden tremor onset or evidence of stepwise deterioration of tremor.
7. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.
8. Subject has clinically significant abnormal physical examination or 12-lead ECG at the Screening or Day -1 visits. Note: A 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. An ECG may be repeated if initial values obtained exceed the limits specified.
9. Subject has a history, presence, and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C antibodies (anti-HCV), or human immunodeficiency virus (HIV) 1 or 2 antibodies.
10. Subject has hypothyroidism. Stable thyroid replacement is acceptable.
11. Subject has used alcohol, caffeine, or nicotine within 3 days prior to the Day -1 visit.
12. Subject has a known allergy to SAGE-217 or its major excipient HPβCD.
13. Subject has exposure to another investigational medication or device within the prior 30 days.
14. Subject has a history of suicidal behavior within 2 years or answers "YES" to questions 3, 4, or 5 on the C-SSRS at the Screening visit or on Day -1 or is currently at risk of suicide in the opinion of the Investigator.
15. Subject has donated one or more units (1 unit = 450 mL) of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing.
16. Subject is unwilling or unable to comply with study procedures.
17. Use of any known strong inhibitors and/or inducers of CYP3A4, as defined in Appendix 2, within the 14 days or 5 half-lives (whichever is longer) or consumed grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.
18. Subject has obstructed venous access and/or has skin disease, rash, acne, or abrasion at venous access site that may affect the ability to obtain a PK sample (eg, artificial cardiac valve, joint replacement).

19. Subject has concurrent or recent exposure (14 days prior to the Day -1 visit) to sedative/hypnotic (eg, opioids) drugs.
20. Subject has hyperthyroidism at screening (based on thyroid-stimulating hormone, thyroxine [T4], and triiodothyronine [T3]) or clinically significant kidney issues in the opinion of the Investigator.

8.3. Entrance Criteria for Part B

The following entrance criteria will be applied prior to administration of blinded study drug in Part B; subjects who require dose adjustments on Days 5, 6, or 7 of Part A will not progress to Part B.

1. Subject must tolerate a dose of ≥10 mg of SAGE-217 in Part A.
2. Subject must have responded to SAGE-217, defined as a 30% reduction from baseline in TETRAS kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) predose on Day 8.

8.4. Subject Withdrawal Criteria

If there is an adverse event or medical reason for the withdrawal, the subject should be followed medically until the condition has either resolved itself or is stable. Details of the reason for withdrawal should be recorded in the subject's case report form (CRF).

Subjects who withdraw should, if possible, have a follow-up examination, including a physical examination, the appropriate investigations, vital signs, and clinical laboratory tests, as outlined for the Day 21 visit (Table 3). If the subject cannot return on Day 21 (Early Termination visit), their visit can be scheduled at an alternative time, at the discretion of the Investigator and subject. All details of this follow-up examination should be recorded in the subject's medical source documents.

8.4.1. Study Drug Withdrawal

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 at the lowest dose;
- Occurrence of pregnancy;
- Intake of nonpermitted concomitant medication;
- Subject noncompliance;
- Significant protocol deviation determined in consultation with the Medical Monitor.

If a subject failed 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 who withdraw or are withdrawn from the study will be replaced only if they withdraw prior to dosing. Subjects who are withdrawn from the study, fail to return or are no longer qualified will not be replaced.

8.4.2. 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.

9. TREATMENT OF SUBJECTS

9.1. Number of Subjects

Approximately 60 subjects with ET will be recruited into the study to yield at least 40 randomized subjects for Part B.

9.2. Treatment Assignment

Study drug will be administered in the morning with food during Part A and Part B.

9.2.1. Part A

Subjects participating in Part A of the study will take study drug (SAGE-217) in an open-label manner. All subjects will start on a 10-mg dose of study drug administered with food in the morning on Day 1. Subjects will receive 20 mg with food on Day 2 and 30 mg with food daily on Days 3 to 7. Dose adjustments may be allowed per the criteria in Section 9.3. The dose tolerated for Days 5, 6, and 7 of the open-label dosing period will be determined to be the maximum dose for that subject.

9.2.2. Part B

Subjects participating in the double-blind, placebo-controlled, randomized withdrawal portion of the study (Part B) will be randomized to SAGE-217 or placebo on Day 8. Subjects randomized to SAGE-217 will receive the maximum dose of SAGE-217 from Part A of the study. Following randomization, subjects will receive 7 days of study drug starting on Day 8.

9.3. Dose Adjustment Criteria

Dose adjustments will only be allowed during the open-label phase of the study (Part A). If at any time the dose is not tolerated in Part A, assessed by occurrence of a severe adverse event judged by the investigator to be related to study drug, the dose on the next day will be reduced to the next lowest dose and continued for the remainder of the open-label dosing period (ie, subjects who are unable to tolerate the 30-mg dose will receive a lower dose of 20 mg, and subjects who are unable to tolerate 20 mg will be given a 10-mg dose). The dose tolerated for Days 5, 6, and 7 of the open-label dosing period will be determined to be the maximum dose for that subject. Subjects who require dose adjustments on Days 5, 6, or 7 of Part A will not progress to Part B.

9.4. Prior/Concomitant Medications and Restrictions

9.4.1. 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 9.4.2.

Record the name, start date (if known), indication for use and whether ongoing or stopped of medications/treatments taken within 2 weeks prior to informed consent and throughout 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.

9.4.2. Prohibited Medications

The drug classes listed in Appendix 1 are not permitted in the 14 days prior to the Day -1 visit and for the duration of the study (up to the Day 28 visit). The list provides non-exhaustive examples of each drug class.

Subjects are not permitted to use alcohol, caffeine, or nicotine within 3 days prior to the Day -1 visit through the Day 21 visit.

For subjects who have previously received primidone or topiramate, a 1-week washout period (prior to Day -1) will be used for subjects with past exposures of ≤1 year and a 2-week washout period (prior to Day -1) will be used for subjects with exposures >1 year. For subjects who have previously received propranolol, a 3-day washout period (prior to Day -1) will be used.

9.5. Treatment Compliance

Investigational product will be prepared by the site pharmacist. The Investigator(s) or designee will record the time and dose of study drug administration in the source documents. Any reasons for non-compliance will also be documented, including:

- Missed 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.

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 clinical Good Manufacturing Practice [GMP] conditions at [redacted]) and further admixed at the clinical site in preparation for dosing. Placebo oral solution will be matched to SAGE-217 study drug.

Detailed instructions for study drug preparation will be provided in the Pharmacy Manual.

10.1.1.1. Batch Formula for 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 by [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 (Kleptose®)	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

10.1.2. SAGE-217 Capsules

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.

Matched placebo capsules containing only the above-listed capsule excipients will be provided. Subjects randomized to placebo treatment will be administered 2 placebo capsules per day.

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. Study drug (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. Study drug 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 and placebo), the Investigator or designee will inspect the medication 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 must be carefully stored at the temperature specified in the Pharmacy Manual (eg, clinical dosing solutions stored at approximately 2 to 8°C for 10 days or room temperature for up to 24 hours after preparation), safely and separately from other drugs.

SAGE-217 Capsules and matched placebo 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. Administration and Study Drug Accountability

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 which 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.

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

10.4.1. Study Drug Administration

Subjects in Part A will receive a 10-mg dose of study drug administered in the morning on Day 1, 20 mg on Day 2, and 30 mg on Days 3 to 7.

Subjects in Part B will receive randomized study drug in the morning on Days 8 to 14.

10.4.2. 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.

10.5. 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 (oral solution only), administration of test article, 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 subject symptom response by a measurement of Kinesia, TETRAS upper limb items, and TETRAS Performance Subscale (items 4, 6, 7, and 8). Quality-of-life assessments include TETRAS ADL, QUEST, and video recording of subjects performing three everyday tasks. Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) and tremor oscillation as assessed by multidimensional accelerometer measurements (ie, raw accelerometer values) will be assessed by the Empatica Wristband E4.

11.1. Kinesia

In order to measure tremor amplitude, subjects will wear a wireless ring motion sensor (Kinesia, Great Lakes Neuro Technologies). The motion sensor uses three orthogonal accelerometers and three orthogonal gyroscopes to monitor three-dimensional motion. Data are then transmitted from the sensor to a computer using Bluetooth technology. These measures of three-dimensional motion for each maneuver are then converted to Kinesia scores, which have been shown to correlate with corresponding clinician-rated TETRAS scores (Giovanni 2010). Each Kinesia score ranges from 0 to 4; higher scores indicate more severe tremor. The Kinesia assessment is completed in conjunction with the TETRAS Performance Subscale Item 4 assessment.

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

11.2. TRG Essential Tremor Rating Assessment Scale (TETRAS) Performance Scale

Item #4 (upper limb tremor) of the TETRAS Performance Subscale will be completed using both the Kinesia device and clinician assessment. Testing should be completed within ±10 minutes of the planned questionnaire time points. All three maneuvers in the upper limb assessments (items 4a, 4b, and 4c) will be completed for both arms, first for the RIGHT arm and then for the LEFT. Predose assessments can be done any time within 2 hours prior to the start of administration of study drug. The Day 21 follow-up visit assessments can be done at any time during the visit.

In Part A, the TETRAS upper limb items will be performed at screening and on Day -1 (three assessments separated by at least 30 minutes); a single assessment of TETRAS upper limb items will be performed predose and 2 and 8 hours (±30 minutes) postdose on Days 1, 2, 3, and 7. In addition, the TETRAS upper limb items will be performed, while wearing the Empatica Wristband E4, on Day -1 and 3 hours (±30 minutes) postdose on Days 1, 2, 3, and 7.

The TETRAS ADL Subscale and Performance Subscale (items 4, 6, 7, and 8) will be performed on Day -1 and predose (±30 minutes) on Day 7. On days when the TETRAS ADL and Performance Subscale are performed, Item # 4 will not be repeated.

In Part B, the TETRAS upper limb items will be performed predose and 2 and 8 hours (±30 minutes) postdose on Days 8, 9, and 14, and anytime during the visit on Day 21. In addition, the TETRAS upper limb items will be performed, while wearing the Empatica Wristband E4, 3 hours (±30 minutes) postdose on Days 8, 9, and 14, and anytime during the visit on Day 21. The TETRAS ADL Subscale and Performance Subscale (items 4, 6, 7, and 8) will be performed predose (±30 minutes) on Day 14 and anytime during the visit on Day 21. On days when the TETRAS ADL Subscale and Performance Subscale are performed, Item #4 will not be repeated.

Note that the TETRAS upper limb scores from the test conducted during screening will be used to determine eligibility and must be ≥2 on each side (left and right) for kinetic tremor and ≥2 on each side (left and right) for either wing beating or forward outstretched postural tremor. A copy of the TETRAS is provided in Appendix 3.

11.3. Empatica Wristband E4

Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) will be assessed by the Empatica Wristband E4. The Empatica Wristband E4 is a wearable device that captures motion-based activity and sympathetic nervous system arousal. In Part A, the Empatica Wristband E4 will be worn during the study visits while in clinic on Days -1, 1, 2, 3, and 7. In Part B, the Empatica Wristband E4 will be worn during the study visits while in clinic on Days 8, 9, 14, and anytime during the visit on Day 21. With the exception of during the TETRAS upper limb assessments, the Empatica Wristband E4 will be worn on the wrist that, of the two arms, exhibits more severe tremor symptoms. During the TETRAS upper limb assessments (Part A: Day -1 and 3 hours (±30 minutes) postdose on Days 1, 2, 3 and 7; Part B: 3 hours (±30 minutes) postdose on Days 8, 9, and 14 and 21), the Empatica Wristband E4 will be worn on the wrist corresponding to the side of the body being assessed. Data from the Empatica Wristband E4 will not be presented in the study report; instead, they will be part of a separate report.

11.4. Quality of Life in Essential Tremor Questionnaire (QUEST)

The QUEST is a brief, 30-item, ET-specific QOL scale in which subjects rate the extent to which tremor impacts a function or state, tremor severity in various body parts, perceived health, and overall QOL (Tröster 2005). The QUEST will be administered on Day -1, Day 7, and on Day 14. A copy of the QUEST is provided in Appendix 4.

11.5. Video Recording

Videos of subjects performing three everyday tasks (drinking a glass of water, fastening a button, and one additional task that the subject experiences difficulty with on a daily basis) will be taken on Day -1 and predose on Day 7 in Part A and predose on Day 14 and anytime during the visit on Day 21 in Part B.

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, and 8 hours postdose on Days 1 and 7 and predose on Days 2, 3, 4, 5, and 6. In Part B, plasma samples for PK analysis will be collected predose on Days 8, 9, 10, 11, 12, 13, and 14. 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 CRF 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. At sites where a -70°C to -80°C freezer is not available, plasma samples may be stored at -20°C prior to being transported for bioanalysis. 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 SAGE-217 will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory.

13. ASSESSMENT OF SAFETY

13.1. Safety and Tolerability Parameters

Safety and tolerability of study drug will be evaluated by vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, SSS, and adverse event reporting. The Bond-Lader Mood Rating Scale and a DEQ-5 will be used to assess mood and perception of drug effects, respectively.

13.1.1. Demographic/Medical History

Age, gender, race, and ethnic origin will be recorded at the Screening visit. A full medical history including medication history will be recorded at the Screening visit.

13.1.2. Vital Signs

Vital signs comprise heart rate, respiratory rate, temperature, and supine (supine for at least 5 minutes prior to the measurement) and standing (for at least 2 to 3 minutes) systolic and diastolic blood pressure.

In Part A, vital signs and pulse oximetry will be performed at screening (vital signs only) and Day -1, predose and at 1, 2, 3, 4, 6, and 8 hours postdose on Days 1, 2, 3, and 4, and predose on Days 5, 6, and 7. In Part B, vital signs (both supine for at least 5 minutes prior to the measurement and standing for at least 2 to 3 minutes) and pulse oximetry will be performed predose on Day 8 and at 1, 2, 3, 4, 6, and 8 hours postdose on Days 8, 9, and 10, predose on Days 11, 12, 13, and 14, and anytime during the visit on Day 21. Vital signs and pulse oximetry assessments will be performed within ±10 minutes of the scheduled times.

13.1.3. Weight and Height

Body weight and height will be measured at the Screening visit.

13.1.4. Physical Examination

A physical examination of all major body systems will be undertaken and recorded at the Screening visit.

13.1.5. Electrocardiogram (ECG)

A supine (supine for at least 5 minutes prior to the measurement) 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, predose and at 1 and 8 hours (±10 minutes) postdose on Days 1, 2, 3, 4, and 7. In Part B, the 12-lead ECG will be assessed at 1 and 8 hours (±10 minutes) postdose on Days 8, 9, 10, and 14, and anytime during the visit on Day 21.

All time points are relative to the time of dosing. ECGs will be performed within ±10 minutes of the predose and 1- and 8-hour time points.

13.1.6. Laboratory Assessments

In Part A, blood and urine samples will be collected for hematology, serum chemistry, and urinalysis at the Screening visit, on Day -1, predose on Day 1, and predose on Day 2. In Part B, blood and urine samples will be collected predose on Day 8 and Day 9 and anytime during the visit on Day 21.

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 13.2.1, and recorded in the eCRF.

13.1.6.1. Hematology

Hematology tests will include complete blood count, 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, AST, and ALT, total protein, and albumin.

Thyroid-stimulating hormone, thyroxine (T4), and triiodothyronine (T3) will be performed at screening to confirm subject eligibility.

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. Drugs Screen and Alcohol Test

A urine sample for assessment of selected drugs (sedative/hypnotics [eg, opioids], cotinine, and caffeine) and a breath sample for alcohol screen will be collected at screening and on Day -1. Results may be obtained through subject history. Subjects who use concomitant sedative/hypnotics will be excluded from the study. Use of alcohol, caffeine, or cotinine is not allowed through Day 21.

13.1.6.5. Virus Serology

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

13.1.6.6. Pregnancy Test

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at the Screening visit and by urine pregnancy test on Day -1, predose on Day 8, and at the follow-up visit on Day 28 in Part B.

13.1.6.7. Exploratory Biochemistry

Optional blood samples will be collected at screening and on Days 3 and 7 and may be analyzed for exploratory biochemistry, where consent is given. Future research may suggest other biochemical markers as candidates for influencing not only response to SAGE-217 but also susceptibility to disorders for which SAGE-217 may be evaluated. Thus, the biochemical research may involve study of additional unnamed biochemical biomarkers, but only as related to disease susceptibility and drug action.

13.1.6.8. Genetic Testing

Where consent is given, an optional genetic sample for biomarker testing will be collected at the Screening visit.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (ie, distribution, safety, tolerability, and efficacy) to SAGE-217. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (eg, cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of SAGE-217 (eg, AKR1C4 [3α-hydroxysteroid dehydrogenase]), genes associated with the γ-aminobutyric acid (GABA) receptor (eg, GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3), and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-217 but also susceptibility to disorders for which SAGE-217 may be evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

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 at screening (lifetime history and past 24 months). In Part A, the "Since Last Visit" C-SSRS form will be completed on Day -1, 8 hours postdose (± 1 hour) on Day 1, predose on Day 4, and on Days 5, 6, and 7. In Part B, the "Since Last Visit" C-SSRS form will be completed 8 hours (± 1 hour) postdose on Days 8, 11, 12, 13, and 14, and anytime during the visits on Days 21 and 28. The C-SSRS is provided in Appendix 5.

13.1.8. Stanford Sleepiness Scale (SSS)

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

In Part A, the SSS will be administered predose and at 1, 2, 3, 4, 6, and 8 hours postdose on Days 1, 2, 3, and 4, and predose only on Days 5, 6, and 7. In Part B, the SSS will be administered predose and 1, 2, 4, 6, and 8 hours postdose on Days 8, 9, 10, 11, 12, 13, and 14, and anytime during the visit on Day 21. All time points are relative to the time of dosing. The SSS is to be performed within ±10 minutes of the scheduled times. The SSS is provided in Appendix 6.

13.1.9. Bond-Lader VAS Mood Scale

Mood will be assessed using the Bond-Lader Mood Rating Scale (Bond 1974). This is a 16-part self-administered questionnaire that employs a 100-mm VAS to explore different aspects of self-reported mood. In Part A, the mood scale will be administered predose and 2 hours (±10 minutes) postdose on Days 1, 2, and 7. In Part B, the mood scale will be administered predose and 2 hours (±10 minutes) postdose on Days 8, 9, 14, and anytime during the visit on Day 21. The Bond-Lader Mood Rating Scale is provided in Appendix 7.

13.1.10. Drug Effects Questionnaire (DEQ-5)

A DEQ-5 (Morean 2013) will be administered as follows:

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

The answers are recorded on a 100-mm VAS, with the answer for each being "Not at all" and "Extremely" at the extremes. There will be options to record "Not applicable" for questions 3 and 4 if no drug effects are felt and for question 5 prior to administration of study medication. The DEQ-5 will be performed 2 hours (±10 minutes) postdose on Days 1 and 7 in Part A and 2 hours (±10 minutes) postdose on Days 8 and 14 in Part B. The DEQ-5 is provided in Appendix 8.

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 causally 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.

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, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics or designee for the duration of the study (from the signing of the ICF through the Day 28 visit [or early termination]).

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. 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, 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.

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. 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.
Probably 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. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

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 through the Day 28 visit (or early termination). 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)

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 28 visit (14 days following the last dose of study drug) or early termination. 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 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.

13.6. Emergency Identification of Study Drug (Part B)

Part B is a double-blind study. The pharmacist responsible for preparing the study drug will be unblinded and will retain an official paper copy of the randomization schedule.

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 eCRF. If the subject or study center personnel (other than pharmacist) have been unblinded, the subject will be terminated from the study.

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 complete at least one dose in Part B and have at least one post-randomization efficacy evaluation.

The evaluable population will consist of all randomized subjects with at least one post-randomization Kinesia assessment.

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

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, race, and ethnicity, and baseline characteristics, such as height, weight, and BMI, will be summarized.

Categorical summaries, such as race and ethnicity, 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, drug, 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. Primary Efficacy Endpoint

The change from randomization (predose on Day 8) in the accelerometer-based Kinesia kinetic tremor combined score (ie, the sum of Kinesia kinetic tremor scores from both sides of the body) at Day 14 will be summarized by treatment group in Part B.

Change from randomization to each assessment in Kinesia kinetic tremor combined score will be analyzed using a mixed effects repeated measures model, including center, treatment, randomization Kinesia kinetic tremor combined score, assessment time point, and time point-by-treatment. All explanatory variables will be treated as fixed effects.

14.5. Secondary Efficacy Endpoints

The change from randomization (predose on Day 8) in the Kinesia upper limb total and individual item scores, TETRAS upper limb total and individual upper limb item scores, and other TETRAS Performance Subscale scores at Day 14 will be summarized by treatment group in Part B.

A mixed effects repeated measures model similar to those described in Section 14.4 will be used for the analysis of change from randomization in the following: Kinesia upper limb total score, Kinesia individual item scores, TETRAS upper limb total score, and TETRAS individual upper limb item scores.

14.6. Exploratory Efficacy Endpoints

The change from randomization (predose on Day 8) in TETRAS ADL scores at Day 14 will be summarized by treatment group in Part B.

QUEST data will be listed by subject, study day, and time point.

14.7. Safety and Tolerability Analyses

Data from vital signs, clinical laboratory measures, ECG, and C-SSRS will be summarized using descriptive statistics by group and time point, where applicable. Continuous endpoints will be summarized with 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.

14.7.1. 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 and relationship to study drug (see Section 13.3).

TEAEs 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 signing of the ICF) through the Day 28 visit will be listed.

14.7.2. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from randomization in vital signs will be evaluated by time point.

14.7.3. Physical Examinations

Screening physical examinations will be documented as done/not done; these results will be listed by subject. Any clinically significant physical examination findings will be recorded as medical history.

14.7.4. 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.

14.7.5. Clinical Laboratory Evaluations

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline and randomization in clinical laboratory measures will be evaluated.

14.7.6. 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.

14.7.7. Stanford Sleepiness Scale (SSS)

Sleepiness data collected on the SSS will be listed for all subjects. Changes in score over time will be represented graphically, and change from Day 1 will be measured.

14.7.8. Bond-Lader VAS Mood Scale

Mood data collected on the Bond-Lader VAS mood scale will be listed by subject, study day, and time point. The scores and change from Day 1 will be summarized by study day and time point.

14.7.9. Drug Effects Questionnaire (DEQ-5)

Results from DEQ-5 will be listed by subject, study day, and time point. The result for each question and change from Day 1 will be summarized by study day and time point.

14.7.10. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and will be coded using World Health Organization-Drug Dictionary Enhanced (WHO-DDE) version 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 within 2 weeks prior to the signing of the ICF. 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 part in which they are being taken. If a concomitant medication assigned to a 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.

14.8. Pharmacokinetic Analysis

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics. Time to reach maximum concentration (t_{max}) will be summarized using 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.

Pharmacokinetic and pharmacodynamic modelling assessment of the relationship between plasma exposure of SAGE-217 and change from baseline in Kinesia scores may be assessed.

14.9. Determination of Sample Size

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

14.10. 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 subject into the study, a representative of Sage Therapeutics or designee will visit the investigational study site to:

- Determine the adequacy of the facilities; and
- 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 CRFs, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject'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 subject (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 CRFs 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 subject 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 CRFs.

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 CRFs 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 trial 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

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21. APPENDICES

Copies of scales and questionnaires included in Appendix 3 through Appendix 7 are for reference only; the rating scales and questionnaires are to be used for actual subject assessment per the Schedule of Events.

APPENDIX 1. 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 28 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 2. STRONG INHIBITORS AND INDUCERS OF CYP3A4

The following known strong inhibitors/inducers of CYP3A4 are not permitted within the 14 days or 5 half-lives (whichever is longer) prior to receiving the first dose of study drug:

Strong inhibitors of CYP3A4:	**Strong inducers of CYP3A4:**
Indinavir	Carbamazepine
Nelfinavir	Efavirenz
Ritonavir	Nevirapine
Clarithromycin	Phenobarbital
Telithromycin	Phenytoin
Iitraconazole	Pioglitazone
Ketoconazole	Rifabutin
Nefazodone	Rifampin
Erythromycin	Troglitazone
Cobistat	Enzalutamide
	Mitotane

APPENDIX 3. TRG ESSENTIAL TREMOR RATING ASSESSMENT SCALE (TETRAS)

TRG ESSENTIAL TREMOR RATING ASSESSMENT SCALE (TETRAS©) V 3.3

Activities of Daily Living Subscale

Rate tremor's impact on activities of daily living (0 - 4 scoring).

1. Speaking
0 = Normal.
1 = Slight voice tremulousness, only when "nervous".
2 = Mild voice tremor. All words easily understood.
3 = Moderate voice tremor. Some words difficult to understand.
4 = Severe voice tremor. Most words difficult to understand.

2. Feeding with a spoon
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with feeding with a spoon.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task, such as using two hands or leaning over.
4 = Severely abnormal. Cannot feed with a spoon.

3. Drinking from a glass
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with drinking from a glass.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.

4. Hygiene
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with hygiene.
2 = Mildly abnormal. Some difficulty but can complete task.
3 = Moderately abnormal. Unable to do most fine tasks such as putting on lipstick or shaving unless changes strategy, such as using two hands or using the less affected hand.
4 = Severely abnormal. Cannot complete hygiene activities independently.

5. Dressing
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with dressing.
2 = Mildly abnormal. Able to do everything but has difficulty due to tremor.
3 = Moderately abnormal. Unable to dress without using strategies such as using Velcro, buttoning shirt before putting it on, andusing shoes with laces.
4 = Severely abnormal. Cannot dress independently.

6. Pouring
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with pouring.
2 = Mildly abnormal. Must be very careful to avoid spilling but may spill occasionally.
3 = Moderately abnormal. Must use two hands or uses other strategies to avoid spilling.
4 = Severely abnormal. Cannot pour.

7. Carrying food trays, plates or similar items
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with carrying food trays, plates or similar items.
2 = Mildly abnormal. Must be very careful to avoid spilling items on food tray.
3 = Moderately abnormal. Uses strategies such as holding tightly against body to carry.
4 = Severely abnormal. Cannot carry food trays or similar items.

8. Using Keys
0 = Normal
1 = Slightly abnormal. Tremor is present but can insert key with one hand without difficulty.
2 = Mildly abnormal. Commonly misses target but still routinely puts key in lock with one hand.
3 = Moderately abnormal. Needs to use two hands or other strategies to put key in lock.
4 = Severely abnormal. Cannot put key in lock.

9. Writing
0 = Normal
1 = Slightly abnormal. Tremor present but does not interfere with writing.
2 = Mildly abnormal. Difficulty writing due to the tremor
3 = Moderately abnormal. Cannot write without using strategies such as holding the writing hand with the other hand, holding pen differently or using large pen.
4 = Severely abnormal. Cannot write.

10. Working: If patient is retired, ask as if they were still working. If the patient is a housewife, ask the question as it relates to housework:
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not affect performance at work or at home.
2 = Mildly abnormal. Tremor interferes with work; able to do everything, but with errors.
3 = Moderately abnormal. Unable to continue working without using strategies such as changing jobs or using special equipment.
4 = Severely abnormal. Cannot perform any job or household work.

11. Overall disability with the most affected task (Name task, e.g. using computer mouse, writing, etc)

Task _____

0 = Normal.
1 = Slightly abnormal. Tremor present but does not affect task.
2 = Mildly abnormal. Tremor interferes with task, but patient is still able to perform task.
3 = Moderately abnormal. Can do task but must use strategies.
4 = Severely abnormal. Cannot do the task.

12. Social Impact

0 = None
1 = Aware of tremor, but it does not affect lifestyle or professional life.
2 = Feels embarrassed by tremor in some social situations or professional meetings.
3 = Avoids participating in some social situations or professional meetings because of tremor.
4 = Avoids participating in most social situations or professional meetings because of tremor.

Performance Subscale

Instructions

Scoring is 0 – 4. For most items, the scores are defined only by whole numbers, but 0.5 increments may be used if you believe the rating is between two whole number ratings and cannot be reconciled to a whole number. Each 0.5 increment in rating is specifically defined for the assessment of upper limb postural and kinetic tremor and the dot approximation task (items 4 and 8). All items of the examination, except standing tremor and heel-knee-shin testing, are performed with the patient seated comfortably. For each item, score the highest peak-to-peak amplitude seen at any point during the exam. Instruct patients not to attempt to suppress the tremor, but to let it come out.

1. Head tremor: The head is rotated fully left and then right for 10s each and is then observed for 10s in mid position. Patient then is instructed to gaze fully to the left and then to the right for 10s each with the head in mid position. The nose or chin should be used as the landmark to rate the largest amplitude excursions during the examination.

   0 = no tremor
   1 = slight tremor (< 0.5 cm)
   2 = mild tremor (0.5- < 2.5 cm)
   3 = moderate tremor (2.5-5 cm)
   4 = severe or disfiguring tremor (> 5 cm)

2. Face (including jaw) tremor: Smile, close eyes, open mouth, purse lips. The highest amplitude of the most involved facial anatomy is scored, regardless of whether it occurs during rest or activation. Repetitive blinking or eye fluttering should not be considered as part of facial tremor.

   0 = no tremor
   1 = slight; barely perceptible tremor
   2 = mild; noticeable tremor
   3 = moderate; obvious tremor, present in most voluntary facial contractions
   4 = severe; gross disfiguring tremor

3. Voice tremor: First ask subject to produce an extended "aaah" sound and eee" sound for 5 seconds each. Then assess speech during normal conversation by asking patients "How do you spend your average day?".

   0 = no tremor
   1 = slight: tremor during aaah or eee, but no tremor during speech
   2 = mild: tremor in "aaah" and "eee" and minimal tremor in speech
   3 = moderate: obvious tremor in speech that is fully intelligible
   4 = severe: some words difficult to understand

4. Upper limb tremor: Tremor is assessed during three maneuvers: forward horizontal reach posture, lateral "wing beating" posture, and finger-nose-finger testing. Each upper limb is assessed and scored individually. The forward horizontal posture is held for 5 seconds. The

lateral wing beating posture is held for 20 seconds. The finger-nose-finger movement is executed three times. Amplitude assessment should be based on the maximum displacement of any part of the hand. For example, the amplitude of a pure supination-pronation tremor, pivoting around the wrist would be assessed at either the thumb or fifth digit.

a. Forward outstretched postural tremor: The upper limb is extended directly forward and parallel to the ground. The wrist should be straight, and the fingers extended and abducted so that they do not touch each other.
b. Lateral "wing beating" postural tremor: The arm is extended laterally, parallel to the ground, the elbow is flexed, and the wrist and fingers are extended so that the fingertip of the extended middle finger is positioned in front of the nose. The fingers are abducted so that they do not touch each other. This posture should be held for 20 seconds, one limb at a time.
c. Kinetic tremor: Subjects extend only their index finger. They then touch a set object or the examiners finger located to the full extent of their reach, which is located at the same height (parallel to the ground) and slightly lateral to the midline. Subjects then touch their own nose (or chin if the tremor is severe) and repeat this back and forth three times. Patients should be instructed to touch the tip of their nose or chin and the examiner's finger tip as precisely as possible. Rapid careless movements should be discouraged. Only the greatest tremor amplitude during the finger-nose-finger movement is assessed. This will typically occur at the nose/chin or at the point of full limb extension (target finger).

For all three hand tremor ratings

0 = no tremor
1 = tremor is barely visible (< 0.5 cm)
1.5 = tremor is visible, but less than 1 cm
2 = tremor is 1- < 3 cm amplitude
2.5 = tremor is 3- < 5 cm amplitude
3 = tremor is 5- < 10 cm amplitude
3.5 = tremor is 10- < 20 cm amplitude
4 = tremor is ≥ 20 cm amplitude

5. Lower limb tremor: Raise each lower limb horizontally and parallel to the ground for 5 seconds. Each lower limb is assessed individually. Then perform a standard heel to shin maneuver with each leg, three times, with patient in supine position. The maximum tremor in either maneuver is scored, and only the limb with the largest tremor is scored. Tremor may emerge from any part of the limb, but tremulous displacement of the foot should be scored as follows:

0 = no tremor
1 = slight: barely perceptible (< 0.5 cm)
2 = mild, less than 1 cm at any point
3 = moderate tremor, less than 5 cm at any point
4 = severe tremor, ≥ 5 cm

6. Archimedes spirals: Demonstrate how to draw Archimedes spiral that approximately fills ¼ of an unlined page of standard (letter) paper. The lines of the spiral should be approximately 1.3 cm (0.5 inch) apart. Then ask the subject to copy the spiral. Test and score each hand

separately. Use a ballpoint pen. The pen should be held such that no part of the limb touches the paper or table. Secure the paper on the table in a location that is suitable for the patient's style of drawing. Score the tremor in the spiral, not the movement of the limb.

0 = normal
1 = slight: tremor barely visible.
2 = mild: obvious tremor
3 = moderate: portions of figure not recognizable.
4 = severe: figure not recognizable

7. Handwriting: Have patient write the standard sentence "This is a sample of my best handwriting" using the dominant hand only. Patients must write cursively (i.e., no printing). They cannot hold or stabilize their hand with the other hand. Use a ballpoint pen. Secure the paper on the table in a location that is suitable for the patient's style of writing. Score the tremor in the writing, not the movement of the limb.

0 = normal
1 = slight: untidy due to tremor that is barely visible.
2 = mild: legible, but with considerable tremor.
3 = moderate: some words illegible.
4 = severe: completely illegible

8. Dot approximation task: The examiner makes a dot or X on a piece of paper and instructs the subject to hold the tip of the pen "as close as possible to the dot or center of the X without touching it (ideally approximately 1 mm), for 10 seconds". Each hand is scored separately.

0 = no tremor
1 = tremor is barely visible (< 0.5 cm)
1.5 = tremor is visible, but less than 1 cm
2 = tremor is 1- < 5 cm amplitude
2.5 = tremor is 3- < 5 cm amplitude
3 = tremor is 5- < 10 cm amplitude
3.5 = tremor is 10- < 20 cm amplitude
4 = tremor is ≥ 20 cm amplitude

9. Standing tremor: Subjects are standing, unaided if possible. The knees are 10-20 cm apart and are flexed 10-20°. The arms are down at the subject's side. Tremor is assessed at any point on the legs or trunk.
0 = no tremor
1 = barely perceptible tremor
2 = obvious but mild tremor, does not cause instability
3 = moderate tremor, impairs stability of stance
4 = severe tremor, unable to stand without assistance

Appendix 4. QUALITY OF LIFE IN ESSENTIAL TREMOR QUESTIONNAIRE (QUEST)

Quality of Life in Essential Tremor Questionnaire (QUEST)

Patient's Name: _____ ID: _____ Date: ____/____/____

Gender: ☐ Male ☐ Female Date of Birth: ____/____/____

Heath Status

In general, how would you rate your overall health? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

Overall Quality of Life

Overall, how would you rate your quality of life? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

General Information

In the past month, has your tremor interfered with your sexual satisfaction?	**Y**	**N**
In the past month, have you had side effects from tremor medications?	Y	N
In the past month, have you been satisfied with the tremor control achieved by your medications?	**Y**	**N**

Which most appropriately describes your work status?

- ☐ Never worked
- ☐ Not working, retired because of tremor
- ☐ Not working, retired NOT due to tremor
- ☐ Working full time
- ☐ Working part time

TREMOR SELF ASSESSMENT

For the purposes of this questionnaire, tremor is defined as uncontrollable shaking or quivering of the body part in question.

On a typical day, how many of your waking hours do you have tremor in ANY body part?

Circle: 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Put a mark in the box to rate the severity of your tremor in each of the body parts listed below.

None - no tremor at any time
Mild - mild tremor not causing difficulty in performing any activities
Moderate - tremor causes difficulty in performing **some** activities
Marked - tremor causes difficulty in performing **most** or **all** activities
Severe - tremor **prevents** performing some activities

		None	Mild	Moderate	Marked	Severe
1.	**Head**	☐	☐	☐	☐	☐
2.	Voice	☐	☐	☐	☐	☐
3.	**Right arm/hand**	☐	☐	☐	☐	☐
4.	Left arm/hand	☐	☐	☐	☐	☐
5.	**Right leg/foot**	☐	☐	☐	☐	☐
6.	Left leg/foot	☐	☐	☐	☐	☐

continued on next page

For each question below, please mark the box which best describes your current situation.

For example: N R ~~S~~ F A

N = Never/No
R = Rarely
S = Sometimes
F = Frequently
A = Always/Yes
NA = Not Applicable

1.	My tremor interferes with my ability to communicate with others.		N R S F A
2.	My tremor interferes with my ability to maintain conversations with others.		N R S F A
3.	It is difficult for others to understand my speech because of my tremor.		N R S F A
4.	My tremor interferes with my job or profession.	NA	N R S F A
5.	I have had to change jobs because of my tremor.	NA	N R S F A
6.	I had to retire or take early retirement because of my tremor.		N A
7.	I am only working part time because of my tremor.	NA	N A
8.	I have had to use special aids or accommodations in order to continue my job due to my tremor.	NA	N R S F A
9.	My tremor has led to financial problems or concerns.		N R S F A
10.	I have lost interest in my hobbies because of my tremor.		N R S F A
11.	I have quit some of my hobbies because of my tremor.		N A
12.	I have had to change or develop new hobbies because of my tremor.		N A
13.	My tremor interferes with my ability to write (for example, writing letters, completing forms).		N R S F A
14.	My tremor interferes with my ability to use a typewriter or computer.	NA	N R S F A
15.	My tremor interferes with my ability to use the telephone (for example, dialing, holding the phone).		N R S F A
16.	My tremor interferes with my ability to fix small things around the house (for example, change light bulbs, minor plumbing, fixing household appliances, fixing broken items).		N R S F A
17.	My tremor interferes with dressing (for example, buttoning, zipping, tying shoes).		N R S F A
18.	My tremor interferes with brushing or flossing my teeth.		N R S F A
19.	My tremor interferes with eating (for example, bringing food to mouth, spilling).		N R S F A
20.	My tremor interferes with drinking liquids (for example, bringing to mouth, spilling, pouring).		N R S F A
21.	My tremor interferes with reading or holding reading material.		N R S F A
22.	My tremor interferes with my relationships with others (for example, my family, friends, coworkers).		N R S F A
23.	My tremor makes me feel negative about myself.		N R S F A
24.	I am embarrassed about my tremor.		N R S F A
25.	I am depressed because of my tremor.		N R S F A
26.	I feel isolated or lonely because of my tremor.		N R S F A
27.	I worry about the future due to my tremor.		N R S F A
28.	I am nervous or anxious.		N R S F A
29.	I use alcohol more frequently than I would like to because of my tremor.		N R S F A
30.	I have difficulty concentrating because of my tremor.		N R S F A

THANK YOU!

APPENDIX 5. COLUMBIA – SUICIDE SEVERITY RATING SCALE (C-SSRS)

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 24 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 24 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	____	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime	Past 24 Months
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.

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C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USorl.doc

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	___

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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 ☐
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 6. STANFORD SLEEPINESS SCALE (SSS)

Stanford Sleepiness Scale

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

E. Hoddes, V. Zarcone, H. Smythe, R. Phillips, W. C. Dement

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APPENDIX 7. BOND-LADER VAS (MOOD RATING SCALE)

1. Please rate the way you feel in terms of the dimensions given below.
2. Regard the line as representing the full range of each dimension.
3. Rate your feelings as they are at the moment.
4. Mark clearly and perpendicularly across each line.

Alert	_____	**Drowsy**
Calm	_____	**Excited**
Strong	_____	**Feeble**
Muzzy	_____	**Clear-headed**
Well-coordinated	_____	**Clumsy**
Lethargic	_____	**Energetic**
Contented	_____	**Discontented**
Troubled	_____	**Tranquil**
Mentally Slow	_____	**Quick-witted**
Tense	_____	**Relaxed**
Attentive	_____	**Dreamy**
Incompetent	_____	**Proficient**
Happy	_____	**Sad**
Antagonistic	_____	**Amicable**
Interested	_____	**Bored**
Withdrawn	_____	**Gregarious**

APPENDIX 8. DRUG EFFECTS QUESTIONNAIRE (DEQ-5)

Instructions: This questionnaire asks about how you are feeling after taking the substance that was given to you. Please draw a mark on the line to show how strongly you are feeling each of the following effects ***right now***. You can mark anywhere on the line, but please draw a vertical line (one that goes straight up and down).

Let's look at an example first.

EXAMPLE: Do you feel dizzy right now?
If you do not feel dizzy, draw a line at NOT AT ALL. If you feel very dizzy, draw a line at EXTREMELY. If you feel somewhere in between, you can draw a mark anywhere along the line between NOT AT ALL and EXTREMELY to indicate how dizzy you are. For example, if you feel a little dizzy, you might draw a line that looks something like the example below.

NOT AT ALL — EXTREMELY

1. Do you FEEL a drug effect right now?

NOT AT ALL — EXTREMELY

2. Are you HIGH right now?

NOT AT ALL — EXTREMELY

3. Do you DISLIKE any of the effects you are feeling right now?

NOT AT ALL — EXTREMELY

4. Do you LIKE any of the effects you are feeling right now?

NOT AT ALL — EXTREMELY

5. Would you like MORE of the drug you took, right now?

NOT AT ALL — EXTREMELY

PROTOCOL NUMBER: 217-ETD-201

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

IND NUMBER: 131,258

Investigational Product	SAGE-217
Clinical Phase	2a
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted], M.S.H.S. [redacted] Phone: [redacted] Email: [redacted]
Medical Monitor	[redacted], M.D., M.P.H. Study Physician Phone: [redacted] Email: [redacted]
Date of Original Protocol	Version 1.0, 19 August 2016
Date of Amendment 1	Version 2.0, 28 October 2016
Date of Amendment 2	Version 3.0, 27 January 2017

PROTOCOL SIGNATURE PAGE

Protocol Number:	217-ETD-201
Product:	SAGE-217 Oral Solution
IND No.:	131,258
Study Phase:	2a
Sponsor:	Sage Therapeutics
Date of Amendment 1:	Version 2.0, 28 October 2016
Date of Amendment 2:	Version 3.0, 27 January 2017

Sponsor Approval

[redacted] 27 Jan 2017

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

Sage Therapeutics

[redacted] 27 Jan 2017

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

Sage Therapeutics

[redacted] 27 Jan 2017

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

Sage Therapeutics

[redacted] 27 Jan 2017

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

Sage Therapeutics

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the Clinical Protocol 217-ETD-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
Sponsor Physician	, M.D., M.P.H. Sage Therapeutics	215 First Street, Suite 220 Cambridge, MA 02142 Cell
Sponsor Signatory	, M.D., Ph.D.	215 First Street, Suite 220 Cambridge, MA 02142 Office: Cell:
Medical Monitor		

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 2a, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of SAGE-217 Oral Solution in the Treatment of Subjects with Essential Tremor (ET)

Study center(s): Up to 25 centers

Phase of development: 2a

Methodology:

This study will assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of SAGE-217 Oral Solution.

There are two parts:

Part A: Open-label with morning dosing (7 days).

All subjects will start on a 10-mg dose of study drug administered with food on Day 1. Subjects will receive 20 mg with food on Day 2 and 30 mg with food daily on Days 3 to 7.

Part B: Double-blind, placebo-controlled, randomized withdrawal with morning dosing (7 days).

In order to qualify for Part B of the study, a subject must tolerate a dose of at least 10 mg of SAGE-217, and the subject must have responded to SAGE-217, defined as a 30% reduction from baseline in the TRG Essential Tremor Rating Assessment Scale (TETRAS) kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) predose on Day 8.

Eligible subjects will be randomized in a 1:1 fashion to SAGE-217 or placebo and will receive their maximum dose as determined in Part A in the morning with food. Subjects randomized to the placebo arm will represent randomized withdrawal (withdrawal from treatment they received in Part A).

Methodology:

Dose adjustments will only be allowed during the open-label phase of the study (Part A). If at any time the dose is not tolerated in Part A, assessed by occurrence of a severe adverse event judged by the investigator to be related to study drug, the dose on the next day will be reduced to the next lowest dose and continued for the remainder of the open-label dosing period (ie, subjects who are unable to tolerate the 30-mg dose will receive a lower dose of 20 mg, and subjects who are unable to tolerate 20 mg will be given a 10-mg dose). The dose tolerated for Days 5, 6, and 7 of the open-label dosing period will be determined to be the maximum dose for that subject. Subjects who require dose adjustments on Days 5, 6, or 7 of Part A will not progress to Part B.

Subjects will be exposed to study drug (SAGE-217 or placebo) for up to 14 days and will be followed for an additional 14 days after the administration of the last dose.

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

Objectives:

Primary:

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

Secondary:

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

- Tremor severity, as assessed by the change from randomization (Day 8) in the Kinesia upper limb total score (ie, the sum of accelerometer-based Kinesia forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores from both sides of the body) and individual item scores at Day 14.
- Tremor severity, as measured by the change from randomization (Day 8) in the TETRAS upper limb total score (ie, the sum of TETRAS Performance Subscale item 4 scores [4a, 4b, and 4c] from both sides of the body) and individual TETRAS Performance Subscale upper limb item scores at Day 14.
- Tremor severity, as assessed by the change from randomization (Day 8) in other TETRAS Performance Subscale scores measured at Day 14.
- Safety and tolerability, as assessed by vital signs measurements, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse event reporting.
- Sleepiness, as assessed by the Stanford Sleepiness Scale (SSS).
- Mood, as assessed by the Bond-Lader visual analogue scale (VAS) Mood Scale scores.
- How the subject feels after taking the study drug as assessed by Drug Effects Questionnaire (DEQ-5) ratings.

In addition, plasma concentrations of SAGE-217 and SAGE-217 metabolites may be measured. Pharmacokinetic parameters, such as area under the concentration-time curve from time zero to last time point (AUC_{0-t}), 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}), and terminal half-life ($t_{1/2}$), will be derived, where appropriate.

Exploratory:

The exploratory objectives of the study are to compare the effect of 7 days administration of SAGE-217 Oral Solution to placebo on:

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

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

Number of subjects (planned):

Up to 60 subjects will be enrolled in Part A to yield at least 40 randomized subjects for Part B.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Subject has signed an informed consent form before any study-specific procedures are performed.
2. Subject must be between 18 and 75 years of age, inclusive.
3. Subject must have a diagnosis of ET, defined as bilateral postural tremor and kinetic tremor, involving hands and forearms, that is visible and persistent and the duration is >5 years prior to screening.
4. Subject must have bilateral TETRAS scores of at least two on each side (left and right) for kinetic tremor and at least two on each side (left and right) for either wing beating or forward outstretched postural tremor.
5. Subject must be willing to discontinue medications taken for the treatment of ET, alcohol, nicotine, and caffeine through Day 21 of the study.
6. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests.
7. Female subjects must be post-menopausal, permanently sterile (eg, bilateral tubal occlusion, hysterectomy, bilateral oophorectomy), or of childbearing potential with a negative pregnancy test, non- breastfeeding, and using two highly effective methods of birth control prior to screening through completion of the last follow-up visit (as defined in Section 8.1). If a subject discontinues early after receiving a dose of study drug, they 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 are defined as follows: hormonal (ie, established use of oral, implantable, injectable, or transdermal hormonal methods of conception); placement of an intrauterine device; placement of an intrauterine system; and mechanical/barrier method of contraception (ie, condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [foam, gel, film, cream or suppository]).
8. Male subjects must agree to practice a highly effective method of birth control while on study drug 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.

9. 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. Subject has presence of abnormal neurological signs other than tremor or Froment's sign.
2. Subject has presence of known causes of enhanced physiological tremor.
3. Subject has concurrent or recent exposure (14 days prior to Day -1 visit) to tremorogenic drugs, as defined in Appendix 1, or the presence of a drug withdrawal state.
4. Subject has had direct or indirect trauma to the nervous system within 3 months before the onset of tremor.
5. Subject has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.).
6. Subject has convincing evidence of sudden tremor onset or evidence of stepwise deterioration of tremor.
7. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.
8. Subject has clinically significant abnormal physical examination or 12-lead ECG at the Screening or Day -1 visits. Note: A 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. An ECG may be repeated if initial values obtained exceed the limits specified.
9. Subject has a history, presence, and/or current evidence of serologic positive results for hepatitis B surface antigen, hepatitis C antibodies, or human immunodeficiency virus 1 or 2 antibodies.
10. Subject has hypothyroidism. Stable thyroid replacement is acceptable.
11. Subject has used alcohol, caffeine, or nicotine within 3 days prior to the Day -1 visit.
12. Subject has a known allergy to SAGE-217 or its major excipient hydroxypropyl-β-cyclodextrin (HPβCD).
13. Subject has exposure to another investigational medication or device within the prior 30 days.
14. Subject has a history of suicidal behavior within 2 years or answers "YES" to questions 3, 4, or 5 on the C-SSRS at the Screening visit or on Day -1 or is currently at risk of suicide in the opinion of the Investigator.
15. Subject has donated one or more units (1 unit = 450 mL) of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing.
16. Subject is unwilling or unable to comply with study procedures.
17. Use of 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, pomegranates, tangelos, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.
18. Subject has obstructed venous access and/or has skin disease, rash, acne, or abrasion at venous access site that may affect the ability to obtain a PK sample (eg, artificial cardiac valve, joint replacement).
19. Subject has concurrent or recent exposure (14 days prior to the Day -1 visit) to sedative/hypnotic (eg, opioids) drugs.

20. Subject has hyperthyroidism at screening (based on thyroid-stimulating hormone, thyroxine [T4], and triiodothyronine [T3]) or clinically significant kidney issues in the opinion of the Investigator.

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 and administered as an approximate 40 mL solution with a 10 mg, 20 mg, or 30 mg dose given once daily in the morning with food.

Duration of treatment:

Screening Duration: approximately 28 days; Treatment Period: 14 days; Follow-up: 14 days

Planned Study Duration per Subject: approximately 56 days

Reference therapy, dosage and mode of administration:

Placebo is available as a solution of 40% HPβCD and 0.0025% sucralose, which is further diluted with Sterile Water for Injection and administered as an approximate 40 mL solution given once daily in the morning with food in Part B.

Criteria for evaluation:

Efficacy:

Tremor severity will be measured by accelerometer-based Kinesia and clinician-rated TETRAS Performance Subscale scores. Quality-of-life will be evaluated using the TETRAS ADL, QUEST, and video recording of subjects performing three everyday tasks. Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) and tremor oscillation will be assessed by the Empatica Wristband E4.

Pharmacokinetics:

Plasma will be collected to assay for concentrations of SAGE-217 and may be assayed for SAGE-217 metabolites, if deemed necessary. The following PK parameters will be derived from the plasma concentrations (where evaluable): AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{½}$.

Safety and Tolerability:

Safety and tolerability of study drug will be evaluated by vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, SSS, and adverse event reporting. The Bond-Lader Mood Rating Scale and a DEQ-5 will be used to assess mood and perception of drug effects, respectively.

Statistical methods:

Study Populations

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 complete at least one dose in Part B and have at least one post-randomization efficacy evaluation.

The evaluable population will consist of all randomized subjects with at least one post-randomization Kinesia assessment.

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

Efficacy Analysis

Efficacy data (including change from randomization values for accelerometer-derived Kinesia and clinician-rated TETRAS scores) will be summarized using appropriate descriptive statistics and listed by subject.

The change from randomization (Day 8) in the Kinesia kinetic tremor combined score (ie, the sum of Kinesia kinetic tremor scores from both sides of the body) at Day 14 will be summarized by treatment. Additionally, the change from randomization in the Kinesia upper limb total score and individual item scores at Day 14 will be summarized by treatment.

The change from randomization in TETRAS upper limb total score, individual TETRAS Performance Subscale upper limb item scores, and other TETRAS Performance Subscale scores at Day 14 will be summarized by treatment.

Pharmacokinetic Analysis

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics and listed by subject. Wherever necessary and appropriate, PK parameters will be dose-adjusted to account for individual differences in dose.

Safety Analysis

Adverse events will be coded using Medical Dictionary for Regulatory Activities™. The overall incidence of adverse events will be displayed by System Organ Class, preferred term, and dose group. Incidence of adverse events will also be presented by maximum severity and relationship to study drug. Data from vital signs, clinical laboratory measures, ECG, and C-SSRS will be summarized using descriptive statistics by dose group, where applicable. Continuous endpoints will be summarized with 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 the same summary 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.

Sample Size

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 3: Schedule of Events: Part B (Randomized Withdrawal)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[o] To include those taken throughout the study.

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

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

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LIST OF TABLES

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
ADL	activities of daily living
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-t}	area under the concentration-time curve from time zero to last time point
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
BMI	body mass index
C_{max}	maximum plasma concentration
CNS	central nervous system
CRF	case report form
CS	clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DEQ-5	Drug Effects Questionnaire
ECG	electrocardiogram
eCRF	electronic CRF
ET	essential tremor
GABA	γ-aminobutyric acid
$GABA_A$	γ-aminobutyric acid-ligand gated chloride channel
$GABA_B$	γ-aminobutyric acid-G protein-coupled
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 Council on Harmonisation

Abbreviation or Specialist Term	Explanation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCS	not clinically significant
NF	National Formulary
PI	Principal Investigator
PK	pharmacokinetic
QOL	quality of life
QTcF	QT interval calculated using the Fridericia method
QUEST	Quality of Life in Essential Tremor Questionnaire
SRC	Safety Review Committee
SSS	Stanford Sleepiness Scale
TEAEs	treatment-emergent adverse events
TETRAS	TRG Essential Tremor Rating Assessment Scale
$t_{1/2}$	terminal half-life
t_{max}	time to reach maximum concentration
USP	United States Pharmacopeia
VAS	visual analogue score
WHO-DDE	World Health Organization-Drug Dictionary Enhanced
WMA	World Medical Association

5. INTRODUCTION

5.1. Background of Essential Tremor and Unmet Medical Need

Essential tremor (ET) is among the most common neurological diseases, with an overall prevalence of 0.9%. Prevalence increases with age and is estimated to be 4.6% in people over 65 years of age (Louis 2010, Deuschl 2011). Essential tremor is largely a bilateral, symmetrical postural or kinetic tremor involving hands and forearms that is visible and persistent. Additional or isolated tremor of the head or lower limbs may occur, but in the absence of abnormal posturing (Deuschl 1998, Habib-ur-Rehman 2000). The onset of tremor has a bimodal distribution, with onset between 15 to 20 and 50 to 70 years. Over time, tremors can become more pronounced and may prevent eating, drinking, and writing, as well as executing personal hygiene like shaving or applying make-up. Voice tremors can be severe enough to inhibit talking and singing in public.

Several lines of evidence suggest that cerebellar dysfunction through the cerebellothalamocortical pathway plays a key role in ET (McAuley 2000, Pinto 2003, Elble 2009, Schnitzler 2009, Deuschl 2009). Thalamotomy and deep brain stimulation of the ventral intermediate nucleus and of the subthalamic nucleus improve ET (Deuschl 2011, Zappia 2013, Rajput 2014). Microscopic cerebellar pathology has been identified, including gliosis, Purkinje cell loss, and increased torpedoes (swellings) in the Purkinje cell axons (Louis 2007, Axelrad 2008, Shill 2008, Louis 2009). Activation studies with positron emission tomography indicate abnormally increased regional cerebral blood flow in the cerebellum both at rest and when tremor is provoked by unilateral arm extension (Boecker 1994, Wills 1996).

Essential tremor is associated with impaired γ-aminobutyric acid (GABA)ergic function (and consequent hyperactivity) in the cerebellum (Málly 1996, Bucher 1997, Louis 2007, Louis 2008, Paris-Robidas 2012). γ-aminobutyric acid, the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (γ-aminobutyric acid-ligand gated chloride channel [$GABA_A$] and γ-aminobutyric acid-G protein-coupled [$GABA_B$]) on target neurons. γ-aminobutyric acid-gated chloride channel receptors, the major class of inhibitory neurotransmitter receptors in the brain, are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents.

Drugs acting on $GABA_A$ receptors, such as primidone, benzodiazepines, or ethanol decrease tremor amplitude, suggesting that altered GABAergic neurotransmission is involved in ET. Postmortem analysis revealed a 35% reduction of $GABA_A$ receptors and a 22% to 31% reduction of $GABA_B$ receptors in the dentate nucleus of cerebella of ET subjects (Paris-Robidas 2012). Reduced levels of GABA in the cerebrospinal fluid are also reported in ET subjects (Málly 1996). Moreover, toxins such as aflatrem, penitrem A, or harmaline have been proposed to induce tremor in rodents by interacting with GABA receptors (Cavanagh 1998, Miwa 2007), and targeted deletion of the α1 subunit of $GABA_A$ receptor in knockout mice exhibits a 15 to 19 Hz action tremor, similar to ET in humans (Kralic 2005).

Consistent with the role of GABA, the majority of therapeutics for ET act by augmenting GABAergic transmission (Louis 2012, Benito-Leon 2007, Pahapill 1999). First-line treatments for ET include the anticonvulsant primidone and the β-adrenergic blocker propranolol (Gorman 1986). Like primidone, gabapentin is an anticonvulsant found to be effective in the treatment of ET (O'Brien 1981, Gironell 1999). The oldest treatment for ET is ethanol, which temporarily ameliorates tremor and is frequently used by subjects to self-medicate; however, chronic use of ethanol for tremor management carries the known risks of alcohol dependence and overuse (Pahwa 2003).

These treatments are moderately effective, reducing, though not resolving, tremor amplitudes in about 50% of the subjects (Schmouth 2014). In addition, one out of three patients abandon treatment because of side effects or poor efficacy (Louis 2010), illustrating that with few feasible treatment options and a range of handicaps in daily living makes ET an area of high unmet medical need.

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 ET. Unlike benzodiazepines that are selective for the γ-subunit-containing subset of $GABA_A$ 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.

5.3. 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 as well as 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 which 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 are clinically complete and final clinical study reports are pending. Discussions of pharmacokinetic (PK) data are limited to the single-ascending dose, food, and essential tremor cohorts from Study 217-CLP-101 and the multiple-ascending dose and drug-drug interaction (DDI) 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 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 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.

Study 217-CLP-102 was a two-part study that assessed the effects of multiple-ascending doses of SAGE-217. 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 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 in an open-label manner to study drug-drug interactions. SAGE-217 is not likely to induce the metabolism of CYP2B6 or CYP3A4 substrates. SAGE-217 was orally bioavailable and suitable for once daily oral dosing at night time with food.

SAGE-217 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 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 (AM or PM) or 35 mg (PM) 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.

There were no clinical efficacy data of SAGE-217 in ET, since the present study is the first study in this indication.

5.4. Potential Risks and Benefits

Protocol 217-ETD-201 is the first clinical study of SAGE-217 Oral Solution in ET evaluating the efficacy of this product. 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. Many compounds that target the $GABA_A$ receptors exhibit clinical efficacy in ET, validating this receptor as a therapeutic target. Given the promising SAGE-547 clinical data 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-escalation design has been chosen to permit titration of treatment effect vs tolerability (adverse events), specifically sedation. Each subject will start with an initial dose of 10 mg to be escalated to 20 mg after a day and then escalated further to 30 mg assuming no tolerability issues. At the end of a 7-day exposure, the maximum dose for the subject will be established as will a protocol specified response. Subjects who are responders and tolerate at least the 10-mg dose for a minimum of 3 days will qualify for the randomization phase (Part B). Given the high medical need and potential for benefit in ET, there is a favorable benefit-risk evaluation to investigate SAGE-217 Oral Solution in ET.

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. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

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

6.2. Secondary Objectives

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

1. Tremor severity as assessed by the change from randomization (Day 8) in the Kinesia upper limb total score (ie, the sum of accelerometer-based Kinesia forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores from both sides of the body) and individual item scores at Day 14.
2. Tremor severity as measured by the change from randomization (Day 8) in TRG Essential Tremor Rating Assessment Scale (TETRAS) upper limb total score (ie, the sum of TETRAS Performance Subscale item 4 scores [4a, 4b, and 4c] from both sides of the body) and individual TETRAS Performance Subscale upper limb item scores at Day 14.
3. Tremor severity as assessed by the change from randomization (Day 8) in other TETRAS Performance Subscale scores measured at Day 14.
4. Safety and tolerability as assessed by vital signs measurements, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse event reporting.
5. Sleepiness as assessed by the SSS.
6. Mood as assessed by the Bond-Lader visual analogue score (VAS) Mood Scale.
7. How the subject feels after taking the study drug as assessed by Drug Effects Questionnaire (DEQ-5) ratings.

In addition, plasma concentrations of SAGE-217 and SAGE-217 metabolites may be measured. Pharmacokinetic parameters, such as area under the concentration-time curve from time zero to last time point (AUC_{0-t}), 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}), and terminal half-life ($t_{1/2}$), will be derived, where appropriate.

6.3. Exploratory Objectives

The exploratory objectives of the study are to compare the effect of 7 days administration of SAGE-217 Oral Solution to placebo on:

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

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

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study is a two-part, multicenter, Phase 2a study to evaluate the efficacy, safety, tolerability, and PK of SAGE-217 Oral Solution in up to 60 adult subjects with ET. Part A of the study is an open-label design with morning dosing for 7 days. Part B of the study is a double-blind, placebo-controlled, randomized withdrawal design. Subjects will be exposed to study drug (SAGE-217 or placebo) for up to 14 days and will be followed for an additional 14 days after the administration of the last dose.

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

The study will be conducted in two parts:

- Part A: Beginning on Day 1, all subjects will receive open-label SAGE-217 in the morning with food (as outlined in Section 9.2) for 7 days. Subjects will receive SAGE-217 10 mg on Day 1, SAGE-217 20 mg on Day 2, and SAGE-217 30 mg from Day 3 to Day 7, with dose adjustments for severe adverse events judged by the Investigator to be related to study drug (Section 9.3).
- Part B: In order to qualify for Part B of the study, a subject must tolerate a dose of ≥10 mg of SAGE-217, and the subject must have responded to SAGE-217, defined as a 30% reduction from baseline in TETRAS kinetic tremor (item 4c) combined score predose on Day 8. Eligible subjects will be randomized in a 1:1 fashion to receive SAGE-217 or placebo for 7 days beginning on Day 8. All doses of study drug will be administered with food as outlined in Section 9.2. Subjects randomized to SAGE-217 or placebo will receive their maximum dose as determined in Part A in the morning with food.

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

7.2. Blinding and Randomization

Part A is open-label with no control group; therefore, there will be no randomization or blinding.

Part B of the study is a double-blind, placebo-controlled, randomized withdrawal design. Subjects who tolerate a dose of ≥10 mg of SAGE-217 in Part A and respond to SAGE-217, defined as a 30% reduction from baseline in TETRAS kinetic tremor combined score predose on Day 8, will be randomly assigned in a 1:1 fashion to receive SAGE-217 or placebo according to

a computer-generated randomization schedule. Once it has been determined that a subject meets eligibility criteria for randomization, the subject will be sequentially assigned a subject number. The unblinded pharmacist will then use this randomization number to prepare and allocate blinded study drug to the subject.

The randomization schedule will be generated prior to the start of the study. The randomization schedule will be generated using SAS V9.2 or later. Only the clinic pharmacist, who is responsible for preparing the solutions, will be given a copy of the randomization schedule. In the event of a medical emergency, the pharmacist may reveal actual solution contents to the investigator, who should also alert Sage of the emergency (see Section 13.6 for more details related to unblinding). In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and on the electronic case report form (eCRF). If the subject or study center personnel (other than pharmacist) have been unblinded, the subject will be terminated from the study.

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

8. SELECTION AND WITHDRAWAL OF SUBJECTS

It is anticipated that up to 60 subjects will be enrolled at up to 25 study centers. The following inclusion and exclusion criteria will be applied during screening for Part A of the study.

8.1. Subject Inclusion Criteria

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

1. Subject has signed an ICF before any study-specific procedures are performed.
2. Subject must be between 18 and 75 years of age, inclusive.
3. Subject must have a diagnosis of ET, defined as bilateral postural tremor and kinetic tremor, involving hands and forearms, that is visible and persistent and the duration is >5 years prior to screening.
4. Subject must have bilateral TETRAS scores of at least two on each side (left and right) for kinetic tremor and at least two on each side (left and right) for either wing beating or forward outstretched postural tremor.
5. Subject must be willing to discontinue medications taken for the treatment of ET, alcohol, nicotine, and caffeine through Day 21 of the study.
6. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests.
7. Female subjects must be post-menopausal, permanently sterile (eg, bilateral tubal occlusion, hysterectomy, bilateral oophorectomy), or of childbearing potential with a negative pregnancy test, non- breastfeeding, and using two highly effective methods of birth control prior to screening through completion of the last follow-up visit. If a subject discontinues early after receiving a dose of study drug, they 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 are defined as follows: hormonal (ie, established use of oral, implantable, injectable, or transdermal hormonal methods of conception); placement of an intrauterine device; placement of an intrauterine system; and mechanical/barrier method of contraception (ie, condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [foam, gel, film, cream or suppository]).
8. Male subjects must agree to practice a highly effective method of birth control while on study drug 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.
9. 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 the following exclusion criteria will be excluded from the study:

1. Subject has presence of abnormal neurological signs other than tremor or Froment's sign.

2. Subject has presence of known causes of enhanced physiological tremor.
3. Subject has or recent exposure (14 days prior to the Day -1 visit) to tremorogenic drugs, as defined in Appendix 1, or the presence of a drug withdrawal state.
4. Subject has had direct or indirect trauma to the nervous system within 3 months before the onset of tremor.
5. Subject has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.).
6. Subject has convincing evidence of sudden tremor onset or evidence of stepwise deterioration of tremor.
7. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.
8. Subject has clinically significant abnormal physical examination or 12-lead ECG at the Screening or Day -1 visits. Note: A 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. An ECG may be repeated if initial values obtained exceed the limits specified.
9. Subject has a history, presence, and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C antibodies (anti-HCV), or human immunodeficiency virus (HIV) 1 or 2 antibodies.
10. Subject has hypothyroidism. Stable thyroid replacement is acceptable.
11. Subject has used alcohol, caffeine, or nicotine within 3 days prior to the Day -1 visit.
12. Subject has a known allergy to SAGE-217 or its major excipient HPβCD.
13. Subject has exposure to another investigational medication or device within the prior 30 days.
14. Subject has a history of suicidal behavior within 2 years or answers “YES” to questions 3, 4, or 5 on the C-SSRS at the Screening visit or on Day -1 or is currently at risk of suicide in the opinion of the Investigator.
15. Subject has donated one or more units (1 unit = 450 mL) of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing.
16. Subject is unwilling or unable to comply with study procedures.
17. Use of 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, pomegranates, tangelos, or St. John's Wort or products containing these within 30 days prior to receiving the first dose of study drug.
18. Subject has obstructed venous access and/or has skin disease, rash, acne, or abrasion at venous access site that may affect the ability to obtain a PK sample (eg, artificial cardiac valve, joint replacement).

19. Subject has concurrent or recent exposure (14 days prior to the Day -1 visit) to sedative/hypnotic (eg, opioids) drugs.
20. Subject has hyperthyroidism at screening (based on thyroid-stimulating hormone, thyroxine [T4], and triiodothyronine [T3]) or clinically significant kidney issues in the opinion of the Investigator.

8.3. Entrance Criteria for Part B

The following entrance criteria will be applied prior to administration of blinded study drug in Part B; subjects who require dose adjustments on Days 5, 6, or 7 of Part A will not progress to Part B.

1. Subject must tolerate a dose of ≥10 mg of SAGE-217 in Part A.
2. Subject must have responded to SAGE-217, defined as a 30% reduction from baseline in TETRAS kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) predose on Day 8.

8.4. Subject Withdrawal Criteria

If there is an adverse event or medical reason for the withdrawal, the subject should be followed medically until the condition has either resolved itself or is stable. Details of the reason for withdrawal should be recorded in the subject's case report form (CRF).

Subjects who withdraw should, if possible, have a follow-up examination, including a physical examination, the appropriate investigations, vital signs, and clinical laboratory tests, as outlined for the Day 21 visit (Table 3). If the subject cannot return on Day 21 (Early Termination visit), their visit can be scheduled at an alternative time, at the discretion of the Investigator and subject. All details of this follow-up examination should be recorded in the subject's medical source documents.

8.4.1. Study Drug Withdrawal

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 at the lowest dose;
- Occurrence of pregnancy;
- Intake of nonpermitted concomitant medication;
- Subject noncompliance;
- Significant protocol deviation determined in consultation with the Medical Monitor.

If a subject failed 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 who withdraw or are withdrawn from the study will be replaced only if they withdraw prior to dosing. Subjects who are withdrawn from the study, fail to return or are no longer qualified will not be replaced.

8.4.2. 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.

9. TREATMENT OF SUBJECTS

9.1. Number of Subjects

Approximately 60 subjects with ET will be recruited into the study to yield at least 40 randomized subjects for Part B.

9.2. Treatment Assignment

Study drug will be administered in the morning with food during Part A and Part B.

9.2.1. Part A

Subjects participating in Part A of the study will take study drug (SAGE-217) in an open-label manner. All subjects will start on a 10-mg dose of study drug administered with food in the morning on Day 1. Subjects will receive 20 mg with food on Day 2 and 30 mg with food daily on Days 3 to 7. Dose adjustments may be allowed per the criteria in Section 9.3. The dose tolerated for Days 5, 6, and 7 of the open-label dosing period will be determined to be the maximum dose for that subject.

9.2.2. Part B

Subjects participating in the double-blind, placebo-controlled, randomized withdrawal portion of the study (Part B) will be randomized to SAGE-217 or placebo on Day 8. Subjects randomized to SAGE-217 will receive the maximum dose of SAGE-217 from Part A of the study. Following randomization, subjects will receive 7 days of study drug starting on Day 8.

9.3. Dose Adjustment Criteria

Dose adjustments will only be allowed during the open-label phase of the study (Part A). If at any time the dose is not tolerated in Part A, assessed by occurrence of a severe adverse event judged by the investigator to be related to study drug, the dose on the next day will be reduced to the next lowest dose and continued for the remainder of the open-label dosing period (ie, subjects who are unable to tolerate the 30-mg dose will receive a lower dose of 20 mg, and subjects who are unable to tolerate 20 mg will be given a 10-mg dose). The dose tolerated for Days 5, 6, and 7 of the open-label dosing period will be determined to be the maximum dose for that subject. Subjects who require dose adjustments on Days 5, 6, or 7 of Part A will not progress to Part B.

9.4. Prior/Concomitant Medications and Restrictions

9.4.1. 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 9.4.2.

Record the name, start date (if known), indication for use and whether ongoing or stopped of medications/treatments taken within 2 weeks prior to informed consent and throughout 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.

9.4.2. Prohibited Medications

The drug classes listed in Appendix 1 are not permitted in the 14 days prior to the Day -1 visit and for the duration of the study (up to the Day 28 visit). The list provides non-exhaustive examples of each drug class.

Subjects are not permitted to use alcohol, caffeine, or nicotine within 3 days prior to the Day -1 visit through the Day 21 visit.

For subjects who have previously received primidone or topiramate, a 1-week washout period (prior to Day -1) will be used for subjects with past exposures of ≤1 year and a 2-week washout period (prior to Day -1) will be used for subjects with exposures >1 year. For subjects who have previously received propranolol, a 3-day washout period (prior to Day -1) will be used.

9.5. Treatment Compliance

Investigational product will be prepared by the site pharmacist. The Investigator(s) or designee will record the time and dose of study drug administration in the source documents. Any reasons for non-compliance will also be documented, including:

- Missed 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.

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 clinical Good Manufacturing Practice [GMP] conditions at [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.

10.2. Batch Formula for 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 by [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 (Kleptose®)	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

10.3. 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.

10.4. Study Drug Storage

Upon receipt of study drug (SAGE-217 and placebo), the Investigator or designee will inspect the medication 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 must be carefully stored at the temperature specified in the Pharmacy Manual (eg, clinical dosing solutions stored at approximately 2 to 8°C for 10 days or room temperature for up to 24 hours 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.

10.5. Administration and Study Drug Accountability

Doses will be prepared as an approximate 40 mL oral solution to be swallowed all at once, followed by approximately 200 mL of water which 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.

10.5.1. Study Drug Administration

Subjects in Part A will receive a 10-mg dose of study drug administered in the morning on Day 1, 20 mg on Day 2, and 30 mg on Days 3 to 7.

Subjects in Part B will receive randomized study drug in the morning on Days 8 to 14.

10.5.2. 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.

10.6. Study Drug Handling and Disposal

The pharmacist or designee for drug accountability is to document the date and time of initial compounding, subsequent admixture, administration of test article, 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 subject symptom response by a measurement of Kinesia, TETRAS upper limb items, and TETRAS Performance Subscale (items 4, 6, 7, and 8). Quality-of-life assessments include TETRAS ADL, QUEST, and video recording of subjects performing three everyday tasks. Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) and tremor oscillation as assessed by multidimensional accelerometer measurements (ie, raw accelerometer values) will be assessed by the Empatica Wristband E4.

11.1. Kinesia

In order to measure tremor amplitude, subjects will wear a wireless ring motion sensor (Kinesia, Great Lakes Neuro Technologies). The motion sensor uses three orthogonal accelerometers and three orthogonal gyroscopes to monitor three-dimensional motion. Data are then transmitted from the sensor to a computer using Bluetooth technology. These measures of three-dimensional motion for each maneuver are then converted to Kinesia scores, which have been shown to correlate with corresponding clinician-rated TETRAS scores (Giovanni 2010). Each Kinesia score ranges from 0 to 4; higher scores indicate more severe tremor. The Kinesia assessment is completed in conjunction with the TETRAS Performance Subscale Item 4 assessment.

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

11.2. TRG Essential Tremor Rating Assessment Scale (TETRAS) Performance Scale

Item #4 (upper limb tremor) of the TETRAS Performance Subscale will be completed using both the Kinesia device and clinician assessment. Testing should be completed within ±10 minutes of the planned questionnaire time points. All three maneuvers in the upper limb assessments (items 4a, 4b, and 4c) will be completed for both arms, first for the RIGHT arm and then for the LEFT. Predose assessments can be done any time within 2 hours prior to the start of administration of solution. The Day 21 follow-up visit assessments can be done at any time during the visit.

In Part A, the TETRAS upper limb items will be performed at screening and on Day -1 (three assessments separated by at least 30 minutes); a single assessment of TETRAS upper limb items will be performed predose and 2 and 8 hours (±30 minutes) postdose on Days 1, 2, 3, and 7. In addition, the TETRAS upper limb items will be performed, while wearing the Empatica Wristband E4, on Day -1 and 3 hours (±30 minutes) postdose on Days 1, 2, 3, and 7.

The TETRAS ADL Subscale and Performance Subscale (items 4, 6, 7, and 8) will be performed on Day -1 and predose (±30 minutes) on Day 7. On days when the TETRAS ADL and Performance Subscale are performed, Item # 4 will not be repeated.

In Part B, the TETRAS upper limb items will be performed predose and 2 and 8 hours (±30 minutes) postdose on Days 8, 9, and 14, and anytime during the visit on Day 21. In addition, the TETRAS upper limb items will be performed, while wearing the Empatica Wristband E4, 3 hours (±30 minutes) postdose on Days 8, 9, and 14, and anytime during the visit on Day 21. The TETRAS ADL Subscale and Performance Subscale (items 4, 6, 7, and 8) will be performed predose (±30 minutes) on Day 14 and anytime during the visit on Day 21. On days when the TETRAS ADL Subscale and Performance Subscale are performed, Item #4 will not be repeated.

Note that the TETRAS upper limb scores from the test conducted during screening will be used to determine eligibility and must be ≥2 on each side (left and right) for kinetic tremor and ≥2 on each side (left and right) for either wing beating or forward outstretched postural tremor. A copy of the TETRAS is provided in Appendix 2.

11.3. Empatica Wristband E4

Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) will be assessed by the Empatica Wristband E4. The Empatica Wristband E4 is a wearable device that captures motion-based activity and sympathetic nervous system arousal. In Part A, the Empatica Wristband E4 will be worn during the study visits while in clinic on Days -1, 1, 2, 3, and 7. In Part B, the Empatica Wristband E4 will be worn during the study visits while in clinic on Days 8, 9, 14, and anytime during the visit on Day 21. With the exception of during the TETRAS upper limb assessments, the Empatica Wristband E4 will be worn on the wrist that, of the two arms, exhibits more severe tremor symptoms. During the TETRAS upper limb assessments (Part A: Day -1 and 3 hours (±30 minutes) postdose on Days 1, 2, 3 and 7; Part B: 3 hours (±30 minutes) postdose on Days 8, 9, and 14 and 21), the Empatica Wristband E4 will be worn on the wrist corresponding to the side of the body being assessed. Data from the Empatica Wristband E4 will not be presented in the study report; instead, they will be part of a separate report.

11.4. Quality of Life in Essential Tremor Questionnaire (QUEST)

The QUEST is a brief, 30-item, ET-specific QOL scale in which subjects rate the extent to which tremor impacts a function or state, tremor severity in various body parts, perceived health, and overall QOL (Tröster 2005). The QUEST will be administered on Day -1, Day 7, and on Day 14. A copy of the QUEST is provided in Appendix 3.

11.5. Video Recording

Videos of subjects performing three everyday tasks (drinking a glass of water, fastening a button, and one additional task that the subject experiences difficulty with on a daily basis) will be taken on Day -1 and predose on Day 7 in Part A and predose on Day 14 and anytime during the visit on Day 21 in Part B.

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, and 8 hours postdose on Days 1 and 7 and predose on Days 2, 3, 4, 5, and 6. In Part B, plasma samples for PK analysis will be collected predose on Days 8, 9, 10, 11, 12, 13, and 14. 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 CRF 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 SAGE-217 will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory.

13. ASSESSMENT OF SAFETY

13.1. Safety and Tolerability Parameters

Safety and tolerability of study drug will be evaluated by vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, SSS, and adverse event reporting. The Bond-Lader Mood Rating Scale and a DEQ-5 will be used to assess mood and perception of drug effects, respectively.

13.1.1. Demographic/Medical History

Age, gender, race, and ethnic origin will be recorded at the Screening visit. A full medical history including medication history will be recorded at the Screening visit.

13.1.2. Vital Signs

Vital signs comprise heart rate, respiratory rate, temperature, and supine (supine for at least 5 minutes prior to the measurement) and standing (for at least 2 to 3 minutes) systolic and diastolic blood pressure.

In Part A, vital signs and pulse oximetry will be performed at screening (vital signs only) and Day -1, predose and at 1, 2, 3, 4, 6, and 8 hours postdose on Days 1, 2, 3, and 4, and predose on Days 5, 6, and 7. In Part B, vital signs (both supine for at least 5 minutes prior to the measurement and standing for at least 2 to 3 minutes) and pulse oximetry will be performed predose on Day 8 and at 1, 2, 3, 4, 6, and 8 hours postdose on Days 8, 9, and 10, predose on Days 11, 12, 13, and 14, and anytime during the visit on Day 21. Vital signs and pulse oximetry assessments will be performed within ±10 minutes of the scheduled times.

13.1.3. Weight and Height

Body weight and height will be measured at the Screening visit.

13.1.4. Physical Examination

A physical examination of all major body systems will be undertaken and recorded at the Screening visit.

13.1.5. Electrocardiogram (ECG)

A supine (supine for at least 5 minutes prior to the measurement) 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, predose and at 1 and 8 hours (±10 minutes) postdose on Days 1, 2, 3, 4, and 7. In Part B, the 12-lead ECG will be assessed at 1 and 8 hours (±10 minutes) postdose on Days 8, 9, 10, and 14, and anytime during the visit on Day 21.

All time points are relative to the time of dosing. ECGs will be performed within ±10 minutes of the predose and 1- and 8-hour time points.

13.1.6. Laboratory Assessments

In Part A, blood and urine samples will be collected for hematology, serum chemistry, and urinalysis at the Screening visit, on Day -1, predose on Day 1, and predose on Day 2. In Part B, blood and urine samples will be collected predose on Day 8 and Day 9 and anytime during the visit on Day 21.

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 13.2.1, and recorded in the eCRF.

13.1.6.1. Hematology

Hematology tests will include complete blood count, 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, AST, and ALT, total protein, and albumin.

Thyroid-stimulating hormone, thyroxine (T4), and triiodothyronine (T3) will be performed at screening to confirm subject eligibility.

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. Drugs Screen and Alcohol Test

A urine sample for assessment of selected drugs (sedative/hypnotics [eg, opioids], cotinine, and caffeine) and a breath sample for alcohol screen will be collected at screening and on Day -1. Results may be obtained through subject history. Subjects who use concomitant sedative/hypnotics will be excluded from the study. Use of alcohol, caffeine, or cotinine is not allowed through Day 21.

13.1.6.5. Virus Serology

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

13.1.6.6. Pregnancy Test

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at the Screening visit and by urine pregnancy test on Day -1, predose on Day 8, and at the follow-up visit on Day 28 in Part B.

13.1.6.7. Exploratory Biochemistry

Optional blood samples will be collected at screening and on Days 3 and 7 and may be analyzed for exploratory biochemistry, where consent is given. Future research may suggest other biochemical markers as candidates for influencing not only response to SAGE-217 but also susceptibility to disorders for which SAGE-217 may be evaluated. Thus, the biochemical research may involve study of additional unnamed biochemical biomarkers, but only as related to disease susceptibility and drug action.

13.1.6.8. Genetic Testing

Where consent is given, an optional genetic sample for biomarker testing will be collected at the Screening visit.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (ie, distribution, safety, tolerability, and efficacy) to SAGE-217. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (eg, cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of SAGE-217 (eg, AKR1C4 [3α-hydroxysteroid dehydrogenase]), genes associated with the γ-aminobutyric acid (GABA) receptor (eg, GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3), and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-217 but also susceptibility to disorders for which SAGE-217 may be evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

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 at screening (lifetime history and past 24 months). In Part A, the “Since Last Visit” C-SSRS form will be completed on Day -1, 8 hours postdose (± 1 hour) on Day 1, predose on Day 4, and on Days 5, 6, and 7. In Part B, the “Since Last Visit” C-SSRS form will be completed 8 hours (± 1 hour) postdose on Days 8, 11,

12, 13, and 14, and anytime during the visits on Days 21 and 28. The C-SSRS is provided in Appendix 4.

13.1.8. Stanford Sleepiness Scale (SSS)

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

In Part A, the SSS will be administered predose and at 1, 2, 3, 4, 6, and 8 hours postdose on Days 1, 2, 3, and 4, and predose only on Days 5, 6, and 7. In Part B, the SSS will be administered predose and 1, 2, 4, 6, and 8 hours postdose on Days 8, 9, 10, 11, 12, 13, and 14, and anytime during the visit on Day 21. All time points are relative to the time of dosing. The SSS is to be performed within ±10 minutes of the scheduled times. The SSS is provided in Appendix 5.

13.1.9. Bond-Lader VAS Mood Scale

Mood will be assessed using the Bond-Lader Mood Rating Scale (Bond 1974). This is a 16-part self-administered questionnaire that employs a 100-mm VAS to explore different aspects of self-reported mood. In Part A, the mood scale will be administered predose and 2 hours (±10 minutes) postdose on Days 1, 2, and 7. In Part B, the mood scale will be administered predose and 2 hours (±10 minutes) postdose on Days 8, 9, 14, and anytime during the visit on Day 21. The Bond-Lader Mood Rating Scale is provided in Appendix 6.

13.1.10. Drug Effects Questionnaire (DEQ-5)

A DEQ-5 (Morean 2013) will be administered as follows:

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

The answers are recorded on a 100-mm VAS, with the answer for each being "Not at all" and "Extremely" at the extremes. There will be options to record "Not applicable" for questions 3 and 4 if no drug effects are felt and for question 5 prior to administration of study medication. The DEQ-5 will be performed 2 hours (±10 minutes) postdose on Days 1 and 7 in Part A and 2 hours (±10 minutes) postdose on Days 8 and 14 in Part B. The DEQ-5 is provided in Appendix 7.

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 causally 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.

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, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics or designee for the duration of the study (from the signing of the ICF through the Day 28 visit [or early termination]).

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. 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, 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.

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. 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.
Probably 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. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

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 through the Day 28 visit (or early termination). 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)

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 28 visit (14 days following the last dose of study drug) or early termination. 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 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.

13.6. Emergency Identification of Study Drug (Part B)

Part B is a double-blind study. The pharmacist responsible for preparing the solutions will be unblinded and will retain an official paper copy of the randomization schedule.

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 eCRF. If the subject or study center personnel (other than pharmacist) have been unblinded, the subject will be terminated from the study.

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 complete at least one dose in Part B and have at least one post-randomization efficacy evaluation.

The evaluable population will consist of all randomized subjects with at least one post-randomization Kinesia assessment.

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

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, race, and ethnicity, and baseline characteristics, such as height, weight, and BMI, will be summarized.

Categorical summaries, such as race and ethnicity, 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, drug, 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. Primary Efficacy Endpoint

The change from randomization (predose on Day 8) in the accelerometer-based Kinesia kinetic tremor combined score (ie, the sum of Kinesia kinetic tremor scores from both sides of the body) at Day 14 will be summarized by treatment group in Part B.

Change from randomization to each assessment in Kinesia kinetic tremor combined score will be analyzed using a mixed effects repeated measures model, including center, treatment, randomization Kinesia kinetic tremor combined score, assessment time point, and time point-by-treatment. All explanatory variables will be treated as fixed effects.

14.5. Secondary Efficacy Endpoints

The change from randomization (predose on Day 8) in the Kinesia upper limb total and individual item scores, TETRAS upper limb total and individual upper limb item scores, and

other TETRAS Performance Subscale scores at Day 14 will be summarized by treatment group in Part B.

A mixed effects repeated measures model similar to those described in Section 14.4 will be used for the analysis of change from randomization in the following: Kinesia upper limb total score, Kinesia individual item scores, TETRAS upper limb total score, and TETRAS individual upper limb item scores.

14.6. Exploratory Efficacy Endpoints

The change from randomization (predose on Day 8) in TETRAS ADL scores at Day 14 will be summarized by treatment group in Part B.

QUEST data will be listed by subject, study day, and time point.

14.7. Safety and Tolerability Analyses

Data from vital signs, clinical laboratory measures, ECG, and C-SSRS will be summarized using descriptive statistics by group and time point, where applicable. Continuous endpoints will be summarized with 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.

14.7.1. 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 and relationship to study drug (see Section 13.3).

TEAEs 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 signing of the ICF) through the Day 28 visit will be listed.

14.7.2. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from randomization in vital signs will be evaluated by time point.

14.7.3. Physical Examinations

Screening physical examinations will be documented as done/not done; these results will be listed by subject. Any clinically significant physical examination findings will be recorded as medical history.

14.7.4. 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.

14.7.5. Clinical Laboratory Evaluations

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline and randomization in clinical laboratory measures will be evaluated.

14.7.6. 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.

14.7.7. Stanford Sleepiness Scale (SSS)

Sleepiness data collected on the SSS will be listed for all subjects. Changes in score over time will be represented graphically, and change from Day 1 will be measured.

14.7.8. Bond-Lader VAS Mood Scale

Mood data collected on the Bond-Lader VAS mood scale will be listed by subject, study day, and time point. The scores and change from Day 1 will be summarized by study day and time point.

14.7.9. Drug Effects Questionnaire (DEQ-5)

Results from DEQ-5 will be listed by subject, study day, and time point. The result for each question and change from Day 1 will be summarized by study day and time point.

14.7.10. Prior and Concomitant Medications

Medications will be recorded at each study visit during the study and will be coded using World Health Organization-Drug Dictionary Enhanced (WHO-DDE) version 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 within 2 weeks prior to the signing of the ICF. 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 part in which they are being taken. If a concomitant medication assigned to a 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.

14.8. Pharmacokinetic Analysis

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics. Time to reach maximum concentration (t_{max}) will be summarized using 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.

Pharmacokinetic and pharmacodynamic modelling assessment of the relationship between plasma exposure of SAGE-217 and change from baseline in Kinesia scores may be assessed.

14.9. Determination of Sample Size

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

14.10. 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 subject into the study, a representative of Sage Therapeutics or designee will visit the investigational study site to:

- Determine the adequacy of the facilities; and
- 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 CRFs, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject'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 subject (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 CRFs 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 subject 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 CRFs.

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 CRFs 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 trial 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

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21. APPENDICES

Copies of scales and questionnaires included in Appendix 2 through Appendix 7 are for reference only; the rating scales and questionnaires are to be used for actual subject assessment per the Schedule of Events.

APPENDIX 1. 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 28 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 2. TRG ESSENTIAL TREMOR RATING ASSESSMENT SCALE (TETRAS)

TRG ESSENTIAL TREMOR RATING ASSESSMENT SCALE (TETRAS©) V 3.3

Activities of Daily Living Subscale

Rate tremor's impact on activities of daily living (0 - 4 scoring).

1. Speaking
0 = Normal.
1 = Slight voice tremulousness, only when "nervous".
2 = Mild voice tremor. All words easily understood.
3 = Moderate voice tremor. Some words difficult to understand.
4 = Severe voice tremor. Most words difficult to understand.

2. Feeding with a spoon
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with feeding with a spoon.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task, such as using two hands or leaning over.
4 = Severely abnormal. Cannot feed with a spoon.

3. Drinking from a glass
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with drinking from a glass.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.

4. Hygiene
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with hygiene.
2 = Mildly abnormal. Some difficulty but can complete task.
3 = Moderately abnormal. Unable to do most fine tasks such as putting on lipstick or shaving unless changes strategy, such as using two hands or using the less affected hand.
4 = Severely abnormal. Cannot complete hygiene activities independently.

5. Dressing
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with dressing.
2 = Mildly abnormal. Able to do everything but has difficulty due to tremor.
3 = Moderately abnormal. Unable to dress without using strategies such as using Velcro, buttoning shirt before putting it on, andusing shoes with laces.
4 = Severely abnormal. Cannot dress independently.

6. Pouring
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with pouring.
2 = Mildly abnormal. Must be very careful to avoid spilling but may spill occasionally.
3 = Moderately abnormal. Must use two hands or uses other strategies to avoid spilling.
4 = Severely abnormal. Cannot pour.

7. Carrying food trays, plates or similar items
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with carrying food trays, plates or similar items.
2 = Mildly abnormal. Must be very careful to avoid spilling items on food tray.
3 = Moderately abnormal. Uses strategies such as holding tightly against body to carry.
4 = Severely abnormal. Cannot carry food trays or similar items.

8. Using Keys
0 = Normal
1 = Slightly abnormal. Tremor is present but can insert key with one hand without difficulty.
2 = Mildly abnormal. Commonly misses target but still routinely puts key in lock with one hand.
3 = Moderately abnormal. Needs to use two hands or other strategies to put key in lock.
4 = Severely abnormal. Cannot put key in lock.

9. Writing
0 = Normal
1 = Slightly abnormal. Tremor present but does not interfere with writing.
2 = Mildly abnormal. Difficulty writing due to the tremor
3 = Moderately abnormal. Cannot write without using strategies such as holding the writing hand with the other hand, holding pen differently or using large pen.
4 = Severely abnormal. Cannot write.

10. Working. If patient is retired, ask as if they were still working. If the patient is a housewife, ask the question as it relates to housework:
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not affect performance at work or at home.
2 = Mildly abnormal. Tremor interferes with work; able to do everything, but with errors.
3 = Moderately abnormal. Unable to continue working without using strategies such as changing jobs or using special equipment.
4 = Severely abnormal. Cannot perform any job or household work.

11. Overall disability with the most affected task (Name task, e.g. using computer mouse, writing, etc)

Task _____

0 = Normal.
1 = Slightly abnormal. Tremor present but does not affect task.
2 = Mildly abnormal. Tremor interferes with task, but patient is still able to perform task.
3 = Moderately abnormal. Can do task but must use strategies.
4 = Severely abnormal. Cannot do the task.

12. Social Impact

0 = None
1 = Aware of tremor, but it does not affect lifestyle or professional life.
2 = Feels embarrassed by tremor in some social situations or professional meetings.
3 = Avoids participating in some social situations or professional meetings because of tremor.
4 = Avoids participating in most social situations or professional meetings because of tremor.

Performance Subscale

Instructions

Scoring is 0 – 4. For most items, the scores are defined only by whole numbers, but 0.5 increments may be used if you believe the rating is between two whole number ratings and cannot be reconciled to a whole number. Each 0.5 increment in rating is specifically defined for the assessment of upper limb postural and kinetic tremor and the dot approximation task (items 4 and 8). All items of the examination, except standing tremor and heel-knee-shin testing, are performed with the patient seated comfortably. For each item, score the highest peak-to-peak amplitude seen at any point during the exam. Instruct patients not to attempt to suppress the tremor, but to let it come out.

1. Head tremor: The head is rotated fully left and then right for 10s each and is then observed for 10s in mid position. Patient then is instructed to gaze fully to the left and then to the right for 10s each with the head in mid position. The nose or chin should be used as the landmark to rate the largest amplitude excursions during the examination.

   0 = no tremor
   1 = slight tremor (< 0.5 cm)
   2 = mild tremor (0.5- < 2.5 cm)
   3 = moderate tremor (2.5-5 cm)
   4 = severe or disfiguring tremor (> 5 cm)

2. Face (including jaw) tremor: Smile, close eyes, open mouth, purse lips. The highest amplitude of the most involved facial anatomy is scored, regardless of whether it occurs during rest or activation. Repetitive blinking or eye fluttering should not be considered as part of facial tremor.

   0 = no tremor
   1 = slight; barely perceptible tremor
   2 = mild: noticeable tremor
   3 = moderate: obvious tremor, present in most voluntary facial contractions
   4 = severe: gross disfiguring tremor

3. Voice tremor: First ask subject to produce an extended "aaah" sound and eee" sound for 5 seconds each. Then assess speech during normal conversation by asking patients "How do you spend your average day?".

   0 = no tremor
   1 = slight: tremor during aaah or eee, but no tremor during speech
   2 = mild: tremor in "aaah" and "eee" and minimal tremor in speech
   3 = moderate: obvious tremor in speech that is fully intelligible
   4 = severe: some words difficult to understand

4. Upper limb tremor: Tremor is assessed during three maneuvers: forward horizontal reach posture, lateral "wing beating" posture, and finger-nose-finger testing. Each upper limb is assessed and scored individually. The forward horizontal posture is held for 5 seconds. The

lateral wing beating posture is held for 20 seconds. The finger-nose-finger movement is executed three times. Amplitude assessment should be based on the maximum displacement of any part of the hand. For example, the amplitude of a pure supination-pronation tremor, pivoting around the wrist would be assessed at either the thumb or fifth digit.

a. Forward outstretched postural tremor: The upper limb is extended directly forward and parallel to the ground. The wrist should be straight, and the fingers extended and abducted so that they do not touch each other.
b. Lateral "wing beating" postural tremor: The arm is extended laterally, parallel to the ground, the elbow is flexed, and the wrist and fingers are extended so that the fingertip of the extended middle finger is positioned in front of the nose. The fingers are abducted so that they do not touch each other. This posture should be held for 20 seconds, one limb at a time.
c. Kinetic tremor: Subjects extend only their index finger. They then touch a set object or the examiners finger located to the full extent of their reach, which is located at the same height (parallel to the ground) and slightly lateral to the midline. Subjects then touch their own nose (or chin if the tremor is severe) and repeat this back and forth three times. Patients should be instructed to touch the tip of their nose or chin and the examiner's finger tip as precisely as possible. Rapid careless movements should be discouraged. Only the greatest tremor amplitude during the finger-nose-finger movement is assessed. This will typically occur at the nose/chin or at the point of full limb extension (target finger).

For all three hand tremor ratings

0 = no tremor
1 = tremor is barely visible (< 0.5 cm)
1.5 = tremor is visible, but less than 1 cm
2 = tremor is 1- < 3 cm amplitude
2.5 = tremor is 3- < 5 cm amplitude
3 = tremor is 5- < 10 cm amplitude
3.5 = tremor is 10- < 20 cm amplitude
4 = tremor is ≥ 20 cm amplitude

5. Lower limb tremor: Raise each lower limb horizontally and parallel to the ground for 5 seconds. Each lower limb is assessed individually. Then perform a standard heel to shin maneuver with each leg, three times, with patient in supine position. The maximum tremor in either maneuver is scored, and only the limb with the largest tremor is scored. Tremor may emerge from any part of the limb, but tremulous displacement of the foot should be scored as follows:

   0 = no tremor
   1 = slight: barely perceptible (< 0.5 cm)
   2 = mild, less than 1 cm at any point
   3 = moderate tremor, less than 5 cm at any point
   4 = severe tremor, ≥ 5 cm

6. Archimedes spirals: Demonstrate how to draw Archimedes spiral that approximately fills ¼ of an unlined page of standard (letter) paper. The lines of the spiral should be approximately 1.3 cm (0.5 inch) apart. Then ask the subject to copy the spiral. Test and score each hand

separately. Use a ballpoint pen. The pen should be held such that no part of the limb touches the paper or table. Secure the paper on the table in a location that is suitable for the patient's style of drawing. Score the tremor in the spiral, not the movement of the limb.

0 = normal
1 = slight: tremor barely visible.
2 = mild: obvious tremor
3 = moderate: portions of figure not recognizable.
4 = severe: figure not recognizable

7. Handwriting: Have patient write the standard sentence "This is a sample of my best handwriting" using the dominant hand only. Patients must write cursively (i.e., no printing). They cannot hold or stabilize their hand with the other hand. Use a ballpoint pen. Secure the paper on the table in a location that is suitable for the patient's style of writing. Score the tremor in the writing, not the movement of the limb.

0 = normal
1 = slight: untidy due to tremor that is barely visible.
2 = mild: legible, but with considerable tremor.
3 = moderate: some words illegible.
4 = severe: completely illegible

8. Dot approximation task: The examiner makes a dot or X on a piece of paper and instructs the subject to hold the tip of the pen "as close as possible to the dot or center of the X without touching it (ideally approximately 1 mm), for 10 seconds". Each hand is scored separately.

0 = no tremor
1 = tremor is barely visible (< 0.5 cm)
1.5 = tremor is visible, but less than 1 cm
2 = tremor is 1- < 3 cm amplitude
2.5 = tremor is 3- < 5 cm amplitude
3 = tremor is 5- < 10 cm amplitude
3.5 = tremor is 10- < 20 cm amplitude
4 = tremor is ≥ 20 cm amplitude

9. Standing tremor: Subjects are standing, unaided if possible. The knees are 10-20 cm apart and are flexed 10-20°. The arms are down at the subject's side. Tremor is assessed at any point on the legs or trunk.
0 = no tremor
1 = barely perceptible tremor
2 = obvious but mild tremor, does not cause instability
3 = moderate tremor, impairs stability of stance
4 = severe tremor, unable to stand without assistance

Appendix 3. QUALITY OF LIFE IN ESSENTIAL TREMOR QUESTIONNAIRE (QUEST)

Quality of Life in Essential Tremor Questionnaire (QUEST)

Patient's Name: _____ ID: _____ Date: ____/____/____

Gender: ☐ Male ☐ Female Date of Birth: ____/____/____

Heath Status

In general, how would you rate your overall health? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

Overall Quality of Life

Overall, how would you rate your quality of life? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

General Information

In the past month, has your tremor interfered with your sexual satisfaction?	**Y**	**N**
In the past month, have you had side effects from tremor medications?	Y	N
In the past month, have you been satisfied with the tremor control achieved by your medications?	**Y**	**N**

Which most appropriately describes your work status?

- ☐ Never worked
- ☐ Not working, retired because of tremor
- ☐ Not working, retired NOT due to tremor
- ☐ Working full time
- ☐ Working part time

TREMOR SELF ASSESSMENT

For the purposes of this questionnaire, tremor is defined as uncontrollable shaking or quivering of the body part in question.

On a typical day, how many of your waking hours do you have tremor in ANY body part?

Circle: 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Put a mark in the box to rate the severity of your tremor in each of the body parts listed below.

None - no tremor at any time
Mild - mild tremor not causing difficulty in performing any activities
Moderate - tremor causes difficulty in performing **some** activities
Marked - tremor causes difficulty in performing **most** or **all** activities
Severe - tremor **prevents** performing some activities

		None	Mild	Moderate	Marked	Severe
1.	**Head**	☐	☐	☐	☐	☐
2.	Voice	☐	☐	☐	☐	☐
3.	**Right arm/hand**	☐	☐	☐	☐	☐
4.	Left arm/hand	☐	☐	☐	☐	☐
5.	**Right leg/foot**	☐	☐	☐	☐	☐
6.	Left leg/foot	☐	☐	☐	☐	☐

continued on next page

For each question below, please mark the box which best describes your current situation.

For example: N R ~~S~~ F A

N = Never/No
R = Rarely
S = Sometimes
F = Frequently
A = Always/Yes
NA = Not Applicable

1.	My tremor interferes with my ability to communicate with others.		N	R	S	F	A
2.	My tremor interferes with my ability to maintain conversations with others.		N	R	S	F	A
3.	It is difficult for others to understand my speech because of my tremor.		N	R	S	F	A
4.	My tremor interferes with my job or profession.	NA	N	R	S	F	A
5.	I have had to change jobs because of my tremor.	NA	N	R	S	F	A
6.	I had to retire or take early retirement because of my tremor.		N				A
7.	I am only working part time because of my tremor.	NA	N				A
8.	I have had to use special aids or accommodations in order to continue my job due to my tremor.	NA	N	R	S	F	A
9.	My tremor has led to financial problems or concerns.		N	R	S	F	A
10.	I have lost interest in my hobbies because of my tremor.		N	R	S	F	A
11.	I have quit some of my hobbies because of my tremor.		N				A
12.	I have had to change or develop new hobbies because of my tremor.		N				A
13.	My tremor interferes with my ability to write (for example, writing letters, completing forms).		N	R	S	F	A
14.	My tremor interferes with my ability to use a typewriter or computer.	NA	N	R	S	F	A
15.	My tremor interferes with my ability to use the telephone (for example, dialing, holding the phone).		N	R	S	F	A
16.	My tremor interferes with my ability to fix small things around the house (for example, change light bulbs, minor plumbing, fixing household appliances, fixing broken items).		N	R	S	F	A
17.	My tremor interferes with dressing (for example, buttoning, zipping, tying shoes).		N	R	S	F	A
18.	My tremor interferes with brushing or flossing my teeth.		N	R	S	F	A
19.	My tremor interferes with eating (for example, bringing food to mouth, spilling).		N	R	S	F	A
20.	My tremor interferes with drinking liquids (for example, bringing to mouth, spilling, pouring).		N	R	S	F	A
21.	My tremor interferes with reading or holding reading material.		N	R	S	F	A
22.	My tremor interferes with my relationships with others (for example, my family, friends, coworkers).		N	R	S	F	A
23.	My tremor makes me feel negative about myself.		N	R	S	F	A
24.	I am embarrassed about my tremor.		N	R	S	F	A
25.	I am depressed because of my tremor.		N	R	S	F	A
26.	I feel isolated or lonely because of my tremor.		N	R	S	F	A
27.	I worry about the future due to my tremor.		N	R	S	F	A
28.	I am nervous or anxious.		N	R	S	F	A
29.	I use alcohol more frequently than I would like to because of my tremor.		N	R	S	F	A
30.	I have difficulty concentrating because of my tremor.		N	R	S	F	A

THANK YOU!

APPENDIX 4. COLUMBIA – SUICIDE SEVERITY RATING SCALE (C-SSRS)

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

C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_AU5.1_eng-USorl.doc

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 24 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 24 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 24 Months
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:

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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

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USorl.doc

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	___

C-SSRS—Since Last Visit (Version 1/14/09)
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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 ☐
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 5. STANFORD SLEEPINESS SCALE (SSS)

Stanford Sleepiness Scale

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

E. Hoddes, V. Zarcone, H. Smythe, R. Phillips, W. C. Dement

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APPENDIX 6. BOND-LADER VAS (MOOD RATING SCALE)

1. Please rate the way you feel in terms of the dimensions given below.
2. Regard the line as representing the full range of each dimension.
3. Rate your feelings as they are at the moment.
4. Mark clearly and perpendicularly across each line.

Alert	_____	**Drowsy**
Calm	_____	**Excited**
Strong	_____	**Feeble**
Muzzy	_____	**Clear-headed**
Well-coordinated	_____	**Clumsy**
Lethargic	_____	**Energetic**
Contented	_____	**Discontented**
Troubled	_____	**Tranquil**
Mentally Slow	_____	**Quick-witted**
Tense	_____	**Relaxed**
Attentive	_____	**Dreamy**
Incompetent	_____	**Proficient**
Happy	_____	**Sad**
Antagonistic	_____	**Amicable**
Interested	_____	**Bored**
Withdrawn	_____	**Gregarious**

APPENDIX 7. DRUG EFFECTS QUESTIONNAIRE (DEQ-5)

Instructions: This questionnaire asks about how you are feeling after taking the substance that was given to you. Please draw a mark on the line to show how strongly you are feeling each of the following effects ***right now***. You can mark anywhere on the line, but please draw a vertical line (one that goes straight up and down).

Let's look at an example first.

EXAMPLE: Do you feel dizzy right now?
If you do not feel dizzy, draw a line at NOT AT ALL. If you feel very dizzy, draw a line at EXTREMELY. If you feel somewhere in between, you can draw a mark anywhere along the line between NOT AT ALL and EXTREMELY to indicate how dizzy you are. For example, if you feel a little dizzy, you might draw a line that looks something like the example below.

1. Do you FEEL a drug effect right now?

2. Are you HIGH right now?

3. Do you DISLIKE any of the effects you are feeling right now?

4. Do you LIKE any of the effects you are feeling right now?

5. Would you like MORE of the drug you took, right now?

1. TITLE PAGE

PROTOCOL NUMBER: 217-ETD-201

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

IND NUMBER: 131,258

Investigational Product	SAGE-217
Clinical Phase	2a
Sponsor	Sage Therapeutics, Inc.
Sponsor Contact	[redacted], M.S.H.S. [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	Version 1.0, 19 August 2016
Date of Amendment One	Version 2.0, 28 October 2016

PROTOCOL SIGNATURE PAGE

Protocol Number:	217-ETD-201
Product:	SAGE-217 Oral Solution
IND No.:	131,258
Study Phase:	2a
Sponsor:	Sage Therapeutics
Date of Amendment One:	Version 2.0 28 October 2016

Sponsor Approval

[redacted] 28 Oct 2016

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

Sage Therapeutics

[redacted] 28 oct 2016

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

Sage Therapeutics

[redacted] 28 oct 2016

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

Sage Therapeutics

[redacted] 28 Oct 2016

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

Sage Therapeutics

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-217. I have read the Clinical Protocol 217-ETD-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
Sponsor Physician	[redacted], M.D., M.P.H. [redacted] Sage Therapeutics [redacted]	215 First Street, Suite 220 Cambridge, MA 02142 Cell: [redacted]
Sponsor Signatory	[redacted], M.D., Ph.D. [redacted] [redacted]	215 First Street, Suite 220 Cambridge, MA 02142 Office: [redacted] Cell: [redacted]
Medical Monitor	[redacted], M.D. [redacted] [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 2a, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of SAGE-217 Oral Solution in the Treatment of Subjects with Essential Tremor (ET)

Study center(s): Up to 30 centers

Phase of development: 2a

Methodology:

This study will assess the efficacy, safety, tolerability, and PK of SAGE-217 Oral Solution.

There are two parts:

Part A: Open-label with morning dosing (7 days).

All subjects will start on a 10 mg dose of study drug administered with food in the morning on Day 1. Subjects will receive 20 mg with food on Day 2 and 30 mg with food daily on Days 3 to 7.

Part B: Double-blind, placebo-controlled, randomized withdrawal with morning and evening dosing (7 days).

In order to qualify for Part B of the study, a subject must tolerate a maximum dose of at least 10 mg of SAGE-217, and the subject must have responded to SAGE-217, defined as a 30% reduction from baseline in the TRG Essential Tremor Rating Assessment Scale (TETRAS) kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) predose on Day 8.

Eligible subjects will be randomized in a 1:1:1 fashion to SAGE-217 morning dosing, SAGE-217 evening dosing, or placebo. In order to preserve the blind, those randomized to SAGE-217 morning dosing will receive placebo for the evening dose, those randomized to SAGE-217 evening dosing will receive placebo for the morning dose, and those randomized to placebo will receive placebo for both morning and evening dosing. Subjects randomized to SAGE-217 will receive their maximum dose as determined in Part A. Subjects randomized to the placebo arm will represent randomized withdrawal (withdrawal from treatment they received in Part A). Subjects will be administered study drug with meals in the morning and in the evening for 7 consecutive days.

Methodology:

Dose adjustments will only be allowed during the open-label phase of the study (Part A). If at any time the dose is not tolerated in Part A, assessed by occurrence of a severe adverse event judged by the investigator to be related to study drug, the dose on the next day will be reduced to the next lowest dose and continued for the remainder of the open-label dosing period (ie, subjects who are unable to tolerate the 30 mg dose will receive a lower dose of 20 mg, and subjects who are unable to tolerate 20 mg will be given a 10 mg dose). The dose tolerated for Days 5, 6, and 7 of the open-label dosing period will be determined to be the maximum dose for that subject. Subjects who require dose adjustments on Days 5, 6, and 7 of Part A will not progress to Part B.

Subjects will be exposed to study drug (SAGE-217 or placebo) for up to 14 days and will be followed for an additional 14 days after the administration of the last dose.

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

Objectives:

Primary:

- The primary objective of this study is to compare the effect of 7 days administration of SAGE-217 Oral Solution to placebo on the change in tremor severity.

Secondary:

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

- Tremor severity, as assessed by the change from randomization (Day 8) in the accelerometer-based Kinesia upper limb total score (ie, the sum of forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores across both sides of the body) and individual item scores at Day 14.
- Tremor severity, as measured by the change from randomization (Day 8) in the TETRAS upper limb total score (ie, the sum of item 4c scores from both sides of the body) and individual TETRAS upper limb item scores at Day 14.
- Tremor severity, as assessed by the change from randomization (Day 8) in TETRAS Performance Subscale scores measured at Day 14.
- Safety and tolerability, as assessed by vital signs measurements, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse event reporting.
- Sleepiness/sedation, as assessed by the Stanford Sleepiness Scale (SSS) and Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores.
- Mood, as assessed by the Bond-Lader visual analogue scale (VAS) Mood Scale scores.
- How the subject feels after taking the study drug as assessed by Drug Effects Questionnaire (DEQ-5) ratings.

In addition, plasma concentrations of SAGE-217 and SAGE-217 metabolites may be measured. Pharmacokinetic (PK) parameters, such as area under the concentration-time curve from time zero to last time point (AUC_{0-t}), 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}), and terminal half-life ($t_{1/2}$), will be derived, where appropriate.

Exploratory:

The exploratory objectives of the study are to compare the effect of 7 days administration of SAGE-217 Oral Solution to placebo on:

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

In addition, PK/pharmacodynamics (PD) modelling assessment of the relationship between plasma exposure of SAGE-217 and change from baseline in accelerometer-based Kinesia scores.

Endpoints:

The primary endpoint of this study is the change from randomization (Day 8) in the accelerometer-based Kinesia kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) at Day 14.

Number of subjects (planned):

Up to 80 subjects will be enrolled in Part A to yield at least 60 randomized subjects for Part B.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Subject has signed an informed consent form before any study-specific procedures are performed.
2. Subject must be between 18 and 75 years of age, inclusive.
3. Subject must have a diagnosis of ET, defined as bilateral postural tremor and kinetic tremor, involving hands and forearms, that is visible and persistent and the duration is >5 years prior to screening.
4. Subject must have bilateral TETRAS scores of at least two on each side (left and right) for kinetic tremor and at least two on each side (left and right) for either wing beating or forward outstretched postural tremor.
5. Subject must be willing to discontinue medications taken for the treatment of ET, alcohol, nicotine, and caffeine through Day 21 of the study.
6. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests.
7. Female subjects must be post-menopausal, permanently sterile (bilateral tubal occlusion), or of childbearing potential with a negative pregnancy test, non- breastfeeding, and using two highly effective methods of birth control prior to screening through completion of the last follow-up visit (as defined in Section 8.1). If a subject discontinues early after receiving a dose of study drug, they must continue this method of birth control for at least 7 days following the last dose of study drug.
8. Male subjects must agree to practice a highly effective method of birth control while on study drug 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.
9. Males must be willing to abstain from sperm donation while on study through 13 weeks after receiving the last dose of study drug.

Exclusion criteria:

1. Subject has presence of abnormal neurological signs other than tremor or Froment's sign.
2. Subject has presence of known causes of enhanced physiological tremor.
3. Subject has concurrent or recent exposure (14 days prior to admission visit) to tremorogenic drugs, as defined in Appendix 1, or the presence of a drug withdrawal state.
4. Subject has had direct or indirect trauma to the nervous system within 3 months before the onset of tremor.
5. Subject has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.).
6. Subject has convincing evidence of sudden tremor onset or evidence of stepwise deterioration of tremor.
7. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.
8. Subject has clinically significant abnormal physical examination or 12-lead ECG at the Screening or Admission Visits. Note: A 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. An ECG may be repeated if initial values obtained exceed the limits specified.
9. Subject has a history, presence, and/or current evidence of serologic positive results for hepatitis B surface antigen, hepatitis C antibodies, or human immunodeficiency virus 1 or 2 antibodies.
10. Subject has hyperthyroidism.
11. Subject has used alcohol, caffeine, or nicotine within 3 days prior to Admission visit.
12. Subject has a known allergy to SAGE-217 and its major excipient hydroxypropyl-β-cyclodextrin (HPβCD).
13. Subject has exposure to another investigational medication or device within the prior 30 days.
14. Subject has a history of suicidal behavior within 2 years or answers "YES" to questions 3, 4, or 5 on the C-SSRS at the Screening Visit or on Day -1 or is currently at risk of suicide in the opinion of the Investigator.
15. Subject has donated one or more units (1 unit = 450 mL) of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing.
16. Subject is unwilling or unable to comply with study procedures.
17. Use of 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.
18. Subject has obstructed venous access and/or has skin disease, rash, acne, or abrasion at venous access site that may affect the ability to obtain a PK sample (eg, artificial cardiac valve, joint replacement).
19. Subject has concurrent or recent exposure (14 days prior to admission visit) to sedative/hypnotic (eg, opioids) drugs.
20. Subject has hyperthyroidism at screening (based on thyroid-stimulating hormone, thyroxine [T4], and triiodothyronine [T3]) or clinically significant kidney issues in the opinion of the Investigator.

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:

Screening Duration: approximately 28 days; Treatment Period: 14 days; Follow-up: 14 days

Planned Study Duration per Subject: approximately 56 days

Reference therapy, dosage and mode of administration:

Placebo will be matched to study drug in Part B.

Criteria for evaluation:

Efficacy:

Transducer measurement of tremor amplitude using an accelerometer and TETRAS Performance Subscale. Quality-of-life will be evaluated using the TETRAS ADL, QUEST, and video recording of subjects performing three everyday tasks. Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) will be assessed by the Empatica Wristband E4.

Pharmacokinetics:

Plasma will be collected to assay for concentrations of SAGE-217 and may be assayed for SAGE-217 metabolites, if deemed necessary. The following PK parameters will be derived from the plasma concentrations (where evaluable): AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, and $t_{½}$.

Safety and Tolerability:

Safety and tolerability of study drug will be evaluated by vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, SSS, MOAA/S scores, and adverse event reporting. The Bond-Lader Mood Rating Scale and a DEQ-5 will be used to assess mood and perception of drug effects, respectively.

Statistical methods:

Study Populations

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 complete at least one dose in Part B and have at least one post-randomization efficacy evaluation.

The evaluable population will consist of all randomized subjects with at least one post-randomization Kinesia assessment.

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

Efficacy Analysis

Efficacy data (including change from randomization values for accelerometer-derived Kinesia and clinician-rated TETRAS scores) will be summarized using appropriate descriptive statistics and listed by subject.

The change from randomization (Day 8) in the accelerometer-based Kinesia kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) at Day 14 will be summarized by treatment. Additionally, the change from randomization in the accelerometer-based Kinesia upper limb total score and individual item scores at Day 14 will be summarized by treatment.

The change from randomization in TETRAS upper limb total score, individual TETRAS upper limb item scores, and TETRAS Performance Subscale scores at Day 14 will be summarized by treatment.

Pharmacokinetic Analysis Pharmacokinetic parameters will be summarized using appropriate descriptive statistics and listed by subject. Wherever necessary and appropriate, PK parameters will be dose-adjusted to account for individual differences in dose.
Safety Analysis Adverse events will be coded using Medical Dictionary for Regulatory Activities™. The overall incidence of adverse events will be displayed by System Organ Class, preferred term, and dose group. Incidence of adverse events will also be presented by maximum severity and relationship to study drug. Data from vital signs, clinical laboratory measures, ECG, and C-SSRS will be summarized using descriptive statistics by dose group, where applicable. Continuous endpoints will be summarized with 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 the same summary 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.
Sample Size Up to 80 subjects will be enrolled in Part A to yield at least 60 randomized subjects for Part B. A total sample size of 51 evaluable subjects (ie, 17 per group) will have 80% power to detect a difference in means of 3.0 on the primary endpoint assuming that the common standard deviation is 3.0 using a 2-group t-test with a 0.05 two-sided significance level. Assuming a 15% non-evaluability rate, 20 subjects per group will be randomized. The number of subjects in each treatment group is also thought to be sufficient to assess preliminary safety and tolerability following multiple doses of SAGE-217 Oral Solution.

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

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

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

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

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

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

[c] An optional blood sample for stress hormone levels, kynurenine biochemistry, and markers of inflammation, where consent is given.

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

[e] Vital signs (both supine for at least 5 minutes prior to the measurement and standing) and pulse oximetry will be performed at screening (vital signs only) and Day -1 (Admission), predose on Day 1 and at 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours postdose on Days 1, 2, and 3, and predose on Days 5, 6, and 7. Vital signs and pulse oximetry assessments will 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 ECGs will be performed at screening, predose on Day 1 and Day 7, and at 1 (±10 minutes), 12, and 24 (±15 minutes) hours postdose on Days 1, 2, 3, and 7.

[g] The C-SSRS will be performed at screening, on Day -1 (Admission), 12 hours postdose on Day 1, predose on Day 4, and on Days 5, 6, and 7. Baseline/Screening version of C-SSRS should be used on day of screening and since last visit version should be used on all subsequent time points.

[h] The SSS will be performed predose on Day 1 and 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours postdose on Days 1, 2, and 3, and predose only on Days 5, 6, and 7. 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] The MOAA/S will be performed predose on Day 1 and 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours postdose on Days 1, 2, and 3, and predose only on Days 5, 6, and 7. 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] The Bond-Lader VAS will be at performed predose on Days 1, 2, and 7.

[k] The DEQ-5 will be performed 2 hours postdose on Days 1 and 7.

[l] Kinesia and TETRAS upper limb subscale will be performed at screening (TETRAS upper limb subscale only), on Day -1 (Admission; three assessments separated by at least 30 minutes); single assessments will be performed predose and 2, 12, and 14 hours postdose on Days 1, 2, and 7. All three tests in the upper limb tremor series of assessments (Item 4) will be completed for both arms, first for the RIGHT arm and then for the LEFT. For each test, the maximum score is four, with a resulting maximum score of 24.

[m] TETRAS (all ADL) will be performed on Day -1 (Admission) and predose on Day 7.

[n] The Empatica Wristband E4 will be worn during the Confinement Periods.

[o] Plasma pharmacokinetic samples (±5 minutes) will be taken predose and 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and predose on Days 3, 4, 5, 6, and 7.

[p] Study drug will be administered in the morning with food during Part A.

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

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

Table 3: Schedule of Events: Part B (Randomized Withdrawal)

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

Visit Days	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Follow-up Day 21±1 day[a]	End of Study Day 28±1 day
Adverse events	X								
Concomitant medications[p]	X								
Videos[q]							X	X	

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

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

[b] Safety laboratory tests will be performed predose (morning and evening doses) on Day 8, Day 9, and on Day 21.

[c] To be performed predose (morning dose) on Day 8 and on Day 28.

[d] For morning dose, vital signs (both supine for at least 5 minutes prior to the measurement and standing) and pulse oximetry will be performed predose on Day 8 and at 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours postdose on Days 8, 9, and 10, predose on Days 12, 13, and 14, and on Day 21. Vital signs and pulse oximetry assessments will 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] 12-lead ECGs will be performed at 1 (±10 minutes), 12, and 24 (±15 minutes) hours postdose on Days 8, 9, and 10, 1 (±10 minutes) and 12 (±15 minutes) hours post morning dose and 1 hour (±10 minutes) post evening dose on Day 14, and on Day 21.

[f] The C-SSRS will be performed 12 hours postdose (morning and evening doses) on Day 8, predose (morning and evening doses) on Day 11, and on Days 12, 13, 14, 21, and 28.

[g] The SSS will be performed predose (morning dose) on Day 8 and 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours postdose (morning dose) and 1, 3, 4, 6, and 8 hours postdose (evening dose) on Days 8, 9, and 10, predose (morning and evening doses) only on Days 12, 13, and 14, and on Day 21. 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] The MOAA/S will be performed predose (morning dose) on Day 8 and 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours postdose (morning dose) and 1, 3, 4, 6, and 8 hours postdose (evening dose) on Days 8, 9, and 10, predose (morning and evening doses) only on Days 12, 13, and 14, and on Day 21. 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] The Bond-Lader VAS will be at performed predose (morning and evening doses) on Days 8, 9, 14, and 21.

[k] The DEQ-5 will be performed 2 hours postdose (morning and evening doses) on Days 8 and 14.

[l] Kinesia and TETRAS upper limb subscale will be performed before morning dose, after morning dose (2 hours post morning dose), before evening dose (12 hours post morning dose), and after evening dose (14 hours post morning dose) on Days 8, 9, and 14, and on Day 21. Item 4c (kinetic tremor) of the TETRAS upper limb subscale will be performed after morning dose (3 hours post morning dose) on Days 8 and 9. All three tests in the upper limb tremor series of assessments (Item 4) will be completed for both arms, first for the RIGHT arm and then for the LEFT. For each test, the maximum score is four, with a resulting maximum score of 24.

[m] TETRAS (all ADL) will be performed predose (morning and evening doses) on Day 14 and on Day 21.

[n] The Empatica Wristband E4 will be worn during the Confinement Period and will be removed prior to discharge from the unit on Day 10. The Empatica device will be worn during the corresponding 3-hour postdose TETRAS upper limb subscale (Item 4c [kinetic tremor]) assessments.

[o] Plasma pharmacokinetic samples (±5 minutes) will be taken 0.25, 0.5, 1, 2, 4, 8 (morning dose only), 12, and 24 hours postdose (morning and evening doses) on Day 8 and predose (morning and evening doses) on Days 10, 11, 12, 13, and 14.

[p] Study drug will be administered in the morning with food during Part A and in the morning and evening (every 12 hours) with food during Part B.

[p] To include those taken throughout the study.

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

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

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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
ADL	activities of daily living
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-t}	area under the concentration-time curve from time zero to last time point
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
BMI	body mass index
C_{max}	maximum plasma concentration
CNS	central nervous system
CRF	case report form
CS	clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DEQ-5	Drug Effects Questionnaire
ECG	electrocardiogram
eCRF	electronic CRF
ET	essential tremor
GABA	γ-aminobutyric acid
$GABA_A$	γ-aminobutyric acid-ligand gated chloride channel
$GABA_B$	γ-aminobutyric acid-G protein-coupled
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 Council on Harmonisation

Abbreviation or Specialist Term	Explanation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
MTD	maximum tolerated dose
NCS	not clinically significant
NF	National Formulary
PI	Principal Investigator
PK	pharmacokinetic
QOL	quality of life
QTcF	QT interval calculated using the Fridericia method
QUEST	Quality of Life in Essential Tremor Questionnaire
SRC	Safety Review Committee
SSS	Stanford Sleepiness Scale
TEAEs	treatment-emergent adverse events
TETRAS	TRG Essential Tremor Rating Assessment Scale
$t_{1/2}$	terminal half-life
t_{max}	time to reach maximum concentration
USP	United States Pharmacopeia
VAS	visual analogue score
WHO	World Health Organization
WMA	World Medical Association

5. INTRODUCTION

5.1. Background of Essential Tremor and Unmet Medical Need

Essential tremor (ET) is among the most common neurological diseases, with an overall prevalence of 0.9%. Prevalence increases with age and is estimated to be 4.6% in people over 65 years of age (Louis 2010, Deuschl 2011). Essential tremor is largely a bilateral, symmetrical postural or kinetic tremor involving hands and forearms that is visible and persistent. Additional or isolated tremor of the head or lower limbs may occur, but in the absence of abnormal posturing (Deuschl 1998, Habib-ur-Rehman 2000). The onset of tremor has a bimodal distribution, with onset between 15 to 20 and 50 to 70 years. Over time, tremors can become more pronounced and may prevent eating, drinking, and writing, as well as executing personal hygiene like shaving or applying make-up. Voice tremors can be severe enough to inhibit talking and singing in public.

Several lines of evidence suggest that cerebellar dysfunction through the cerebellothalamocortical pathway plays a key role in ET (McAuley 2000; Pinto 2003; Elble 2009, Schnitzler 2009, Deuschl 2009). Thalamotomy and deep brain stimulation of the ventral intermediate nucleus and of the subthalamic nucleus improve ET (Deuschl 2011, Zappia 2013, Rajput 2014). Microscopic cerebellar pathology has been identified, including gliosis, Purkinje cell loss, and increased torpedoes (swellings) in the Purkinje cell axons (Louis 2007, Axelrad 2008, Shill 2008, Louis 2009). Activation studies with positron emission tomography indicate abnormally increased regional cerebral blood flow in the cerebellum both at rest and when tremor is provoked by unilateral arm extension (Boecker 1994, Wills 1996).

Essential tremor is associated with impaired γ-aminobutyric acid (GABA)ergic function (and consequent hyperactivity) in the cerebellum (Málly 1996, Bucher 1997, Louis 2007, Louis 2008, Paris-Robidas 2012). γ-aminobutyric acid, the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (γ-aminobutyric acid-ligand gated chloride channel [$GABA_A$] and γ-aminobutyric acid-G protein-coupled [$GABA_B$]) on target neurons. γ-aminobutyric acid-gated chloride channel receptors, the major class of inhibitory neurotransmitter receptors in the brain, are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents.

Drugs acting on $GABA_A$ receptors, such as primidone, benzodiazepines, or ethanol decrease tremor amplitude, suggesting that altered GABAergic neurotransmission is involved in ET. Postmortem analysis revealed a 35% reduction of $GABA_A$ receptors and a 22% to 31% reduction of $GABA_B$ receptors in the dentate nucleus of cerebella of ET subjects (Paris-Robidas 2012). Reduced levels of GABA in the cerebrospinal fluid are also reported in ET subjects (Málly 1996). Moreover, toxins such as aflatrem, penitrem A, or harmaline have been proposed to induce tremor in rodents by interacting with GABA receptors (Cavanagh 1998; Miwa 2007), and targeted deletion of the α1 subunit of $GABA_A$ receptor in knockout mice exhibits a 15 to 19 Hz action tremor, similar to ET in humans (Kralic 2005).

Consistent with the role of GABA, the majority of therapeutics for ET act by augmenting GABAergic transmission (Louis 2012, Benito-Leon 2007, Pahapill 1999). First-line treatments for ET include the anticonvulsant primidone and the β-adrenergic blocker propranolol (Gorman 1986). Like primidone, gabapentin is an anticonvulsant found to be effective in the treatment of ET (O'Brien 1981; Gironell 1999). The oldest treatment for ET is ethanol, which temporarily ameliorates tremor and is frequently used by subjects to self-medicate; however, chronic use of ethanol for tremor management carries the known risks of alcohol dependence and overuse (Pahwa 2003).

These treatments are moderately effective, reducing, though not resolving, tremor amplitudes in about 50% of the subjects (Schmouth 2014). In addition, one out of three patients abandon treatment because of side effects or poor efficacy (Louis 2010), illustrating that with few feasible treatment options and a range of handicaps in daily living makes ET an area of high unmet medical need.

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 ET. Unlike benzodiazepines that are selective for the γ-subunit-containing subset of $GABA_A$ 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.

5.3. 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 as well as 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 which 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 are clinically complete and final clinical study reports are pending. Discussions of pharmacokinetic (PK) data are limited to the single-ascending dose, food, and essential tremor cohorts from Study 217-CLP-101 and the multiple-ascending dose and drug-drug interaction (DDI) 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 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 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.

Study 217-CLP-102 was a two-part study that assessed the effects of multiple-ascending doses of SAGE-217. 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 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 in an open-label manner to study drug-drug interactions. SAGE-217 is not likely to induce the metabolism of CYP2B6 or CYP3A4 substrates. SAGE-217 was orally bioavailable and suitable for once daily oral dosing at night time with food.

SAGE-217 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 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 (AM or PM) or 35 mg (PM) 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.

There were no clinical efficacy data of SAGE-217 in ET, since the present study is the first study in this indication.

5.4. Potential Risks and Benefits

Protocol 217-ETD-201 is the first clinical study of SAGE-217 Oral Solution in ET evaluating the efficacy of this product. 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. Many compounds that target the $GABA_A$ receptors exhibit clinical efficacy in ET, validating this receptor as a therapeutic target. Given the promising SAGE-547 clinical data 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-escalation design has been chosen to permit titration of treatment effect vs tolerability (adverse events), specifically sedation. Each subject will start with an initial dose of 10 mg to be escalated to 20 mg after a day and then escalated further to 30 mg assuming no tolerability issues. At the end of a 7-day exposure, the maximum dose for the subject will be established as will a protocol specified response. Subjects who are responders and tolerate at least the 10 mg dose for a minimum of 3 days will qualify for the randomization phase (Part B). Given the high medical need and potential for benefit in ET, there is a favorable benefit-risk evaluation to investigate SAGE-217 Oral Solution in ET.

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. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective of this study is to compare the effect of 7 days administration of SAGE-217 Oral Solution to placebo on the change in tremor severity.

The primary endpoint of this study is the change from randomization (Day 8) in the accelerometer-based Kinesia kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) at Day 14.

6.2. Secondary Objectives

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

1. Tremor severity as assessed by the change from randomization (Day 8) in the accelerometer-based Kinesia upper limb total score (ie, the sum of forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores across both sides of the body) and individual item scores at Day 14.
2. Tremor severity as measured by the change from randomization (Day 8) in TRG Essential Tremor Rating Assessment Scale (TETRAS) upper limb total score (ie, the sum of item 4c scores from both sides of the body) and individual TETRAS upper limb item scores at Day 14.
3. Tremor severity as assessed by the change from randomization (Day 8) in TETRAS Performance Subscale scores measured at Day 14.
4. Safety and tolerability as assessed by vital signs measurements, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse event reporting.
5. Sleepiness/sedation as assessed by the SSS and MOAA/S scores.
6. Mood as assessed by the Bond-Lader visual analogue score (VAS) Mood Scale.
7. How the subject feels after taking the study drug as assessed by Drug Effects Questionnaire (DEQ-5) ratings.

In addition, plasma concentrations of SAGE-217 and SAGE-217 metabolites may be measured. Pharmacokinetic parameters, such as area under the concentration-time curve from time zero to last time point (AUC_{0-t}), 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}), and terminal half-life ($t_{1/2}$), will be derived, where appropriate.

6.3. Exploratory Objectives

The exploratory objectives of the study are to compare the effect of 7 days administration of SAGE-217 Oral Solution to placebo on:

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

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

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study is a two-part, multicenter, Phase 2a study to evaluate the efficacy, safety, tolerability, and PK of SAGE-217 Oral Solution in up to 80 adult subjects with ET. Part A of the study is an open-label design with morning dosing for 7 days. Part B of the study is a double-blind, placebo-controlled, randomized withdrawal design. Subjects will be exposed to study drug (SAGE-217 or placebo) for up to 14 days and will be followed for an additional 14 days after the administration of the last dose.

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

The study will be conducted in two parts:

- Part A: Beginning on Day 1, all subjects will receive open-label SAGE-217 in the morning with food (as outlined in Section 9.2) for 7 days. Subjects will receive SAGE-217 10 mg on Day 1, SAGE-217 20 mg on Day 2, and SAGE-217 30 mg from Day 3 to Day 7, with dose adjustments for severe adverse events judged by the Investigator to be related to study drug (Section 9.3). Subjects will be confined on Day -1 through Day 3.
- Part B: In order to qualify for Part B of the study, a subject must tolerate a maximum dose of ≥10 mg of SAGE-217, and the subject must have responded to SAGE-217, defined as a 30% reduction from baseline in TETRAS kinetic tremor combined score predose on Day 8. Eligible subjects will be randomized in a 1:1:1 fashion to receive SAGE-217 in the morning or in the evening or to receive placebo for 7 days beginning on Day 8. All doses of study drug will be administered with food as outlined in Section 9.2. Subjects randomized to SAGE-217 will receive their maximum dose as determined in Part A. In order to preserve the blind, those randomized to SAGE-217 in the morning will receive placebo in the evening, those randomized to receive SAGE-217 in the evening will receive placebo in the morning, and those randomized to receive placebo will receive placebo in both morning and evening. Subjects randomized to the placebo arm will represent randomized withdrawal (ie, withdrawal from treatment they received in Part A). Subjects will be confined on Day 7 through Day 10.

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

7.2. Blinding and Randomization

Part A is open-label with no control group; therefore, there will be no randomization or blinding.

Part B of the study is a double-blind, placebo-controlled, randomized withdrawal study. Subjects who tolerate a maximum dose of ≥10 mg of SAGE-217 in Part A and respond to SAGE-217, defined as a 30% reduction from baseline in TETRAS kinetic tremor combined score predose on Day 8, will be randomly assigned in a 1:1:1 fashion to receive SAGE-217 in the morning or in the evening or placebo according to a computer-generated randomization schedule. Once it has been determined that a subject meets eligibility criteria, the subject will be sequentially assigned a subject number from the randomization schedule provided to the unblinded pharmacist. Subject identification numbers will consist of the site number (eg, "01") followed by numbering starting with double zero (eg, 01-001, 01-002, 01-003, etc.).

A randomization schedule will be generated prior to the start of the study. The randomization schedule will be generated using SAS V9.2 or later. Only the clinic pharmacist, who is responsible for preparing the solutions, will be given a copy of the randomization schedule. In the event of a medical emergency, the pharmacist may reveal actual solution contents to the investigator, who should also alert Sage of the emergency (see Section 13.6 for more details related to unblinding). In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and on the electronic case report form (eCRF). If the subject or study center personnel (other than pharmacist) have been unblinded, the subject will be terminated from the study.

In order to preserve the blind in Part B, those randomized to SAGE-217 morning dosing will receive placebo for the evening dose, those randomized to SAGE-217 evening dosing will receive placebo for the morning dose, and those randomized to placebo will receive placebo for both morning and evening dosing. Subjects randomized to SAGE-217 will receive their maximum dose as determined in Part A. Subjects randomized to the placebo arm will represent randomized withdrawal (withdrawal from treatment they received in Part A).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

It is anticipated that up to 80 subjects will be enrolled at up to 30 study centers. The following inclusion and exclusion criteria will be applied during screening for Part A of the study.

8.1. Subject Inclusion Criteria

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

1. Subject has signed an ICF before any study-specific procedures are performed.
2. Subject must be between 18 and 75 years of age, inclusive.
3. Subject must have a diagnosis of ET, defined as bilateral postural tremor and kinetic tremor, involving hands and forearms, that is visible and persistent and the duration is >5 years prior to screening.
4. Subject must have bilateral TETRAS scores of at least two on each side (left and right) for kinetic tremor and at least two on each side (left and right) for either wing beating or forward outstretched postural tremor.
5. Subject must be willing to discontinue medications taken for the treatment of ET, alcohol, nicotine, and caffeine through Day 21 of the study.
6. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests.
7. Female subjects must be post-menopausal, permanently sterile (bilateral tubal occlusion), or of childbearing potential with a negative pregnancy test, non- breastfeeding, and using two highly effective methods of birth control prior to screening through completion of the last follow-up visit. If a subject discontinues early after receiving a dose of study drug, they 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 are defined as follows: hormonal (ie, established use of oral, implantable, injectable, or transdermal hormonal methods of conception); placement of an intrauterine device; placement of an intrauterine system; and mechanical/barrier method of contraception (ie, condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [foam, gel, film, cream or suppository]).
8. Male subjects must agree to practice a highly effective method of birth control while on study drug 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.
9. Males must be willing to abstain from sperm donation while on study through 13 weeks after receiving the last dose of study drug.

8.2. Subject Exclusion Criteria

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

1. Subject has presence of abnormal neurological signs other than tremor or Froment's sign.

2. Subject has presence of known causes of enhanced physiological tremor.
3. Subject has or recent exposure (14 days prior to admission visit) to tremorogenic drugs, as defined in Appendix 1, or the presence of a drug withdrawal state.
4. Subject has had direct or indirect trauma to the nervous system within 3 months before the onset of tremor.
5. Subject has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.).
6. Subject has convincing evidence of sudden tremor onset or evidence of stepwise deterioration of tremor.
7. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.
8. Subject has clinically significant abnormal physical examination or 12-lead ECG at the Screening or Admission Visits. Note: A 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. An ECG may be repeated if initial values obtained exceed the limits specified.
9. Subject has a history, presence, and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C antibodies (anti-HCV), or human immunodeficiency virus (HIV) 1 or 2 antibodies.
10. Subject has hyperthyroidism.
11. Subject has used alcohol, caffeine, or nicotine within 3 days prior to Admission visit.
12. Subject has a known allergy to SAGE-217 and its major excipient HPβCD.
13. Subject has exposure to another investigational medication or device within the prior 30 days.
14. Subject has a history of suicidal behavior within 2 years or answers “YES” to questions 3, 4, or 5 on the C-SSRS at the Screening Visit or on Day -1 or is currently at risk of suicide in the opinion of the Investigator.
15. Subject has donated one or more units (1 unit = 450 mL) of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing.
16. Subject is unwilling or unable to comply with study procedures.
17. Use of 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.
18. Subject has obstructed venous access and/or has skin disease, rash, acne, or abrasion at venous access site that may affect the ability to obtain a PK sample (eg, artificial cardiac valve, joint replacement).

19. Subject has concurrent or recent exposure (14 days prior to admission visit) to sedative/hypnotic (eg, opioids) drugs.
20. Subject has hyperthyroidism at screening (based on thyroid-stimulating hormone, thyroxine [T4], and triiodothyronine [T3]) or clinically significant kidney issues in the opinion of the Investigator.

8.3. Entrance Criteria for Part B

The following entrance criteria will be applied prior to administration of blinded study drug in Part B; subjects who require dose adjustments on Days 5, 6, and 7 of Part A will not progress to Part B.

1. Subject must tolerate a maximum dose of ≥10 mg of SAGE-217 in Part A.
2. Subject must have responded to SAGE-217, defined as a 30% reduction from baseline in TETRAS kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) predose on Day 8.

8.4. Subject Withdrawal Criteria

If there is an adverse event or medical reason for the withdrawal, the subject should be followed medically until the condition has either resolved itself or is stable. Details of the reason for withdrawal should be recorded in the subject's case report form (CRF).

Subjects who withdraw should, if possible, have a follow-up examination, including a physical examination, the appropriate investigations, vital signs, and clinical laboratory tests, as outlined for the Day 21 visit (Table 3). All details of this follow-up examination should be recorded in the subject's medical source documents.

8.4.1. Study Drug Withdrawal

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 failed 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 will be replaced only if they withdraw prior to dosing. Subjects who are withdrawn from the study, fail to return or are no longer qualified will not be replaced.

8.4.2. 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.

9. TREATMENT OF SUBJECTS

9.1. Number of Subjects

Approximately 80 subjects with ET will be recruited into the study to yield at least 60 randomized subjects for Part B.

9.2. Treatment Assignment

Study drug will be administered in the morning with food during Part A and in the morning and evening (every 12 hours) with food during Part B. Food intake was standardized as specified by the Sponsor.

9.2.1. Part A

Subjects participating in Part A of the study will take study drug (SAGE-217) in an open-label manner. All subjects will start on a 10 mg dose of study drug administered with food in the morning on Day 1. Subjects will receive 20 mg with food on Day 2 and 30 mg with food daily on Days 3 to 7. Dose adjustments will only be allowed 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 (Section 9.3). The dose tolerated for Days 5, 6, and 7 of the open-label dosing period will be determined to be the maximum dose for that subject.

9.2.2. Part B

Subjects participating in the double-blind, placebo-controlled, randomized withdrawal portion of the study (Part B) will be randomized to SAGE-217 morning dosing, SAGE-217 evening dosing, or placebo. Subjects randomized to SAGE-217 will receive the maximum dose of SAGE-217 from Part A of the study. Following randomization, subjects will receive 7 days of study drug starting on Day 8.

9.3. Dose Adjustment Criteria

Dose adjustments will only be allowed during the open-label phase of the study (Part A). If at any time the dose is not tolerated in Part A, assessed by occurrence of a severe adverse event judged by the investigator to be related to study drug, the dose on the next day will be reduced to the next lowest dose and continued for the remainder of the open-label dosing period (ie, subjects who are unable to tolerate the 30 mg dose will receive a lower dose of 20 mg, and subjects who are unable to tolerate 20 mg will be given a 10 mg dose). The dose tolerated for Days 5, 6, and 7 of the open-label dosing period will be determined to be the maximum dose for that subject. Subjects who require dose adjustments on Days 5, 6, and 7 of Part A will not progress to Part B.

9.4. Prior/Concomitant Medications and Restrictions

9.4.1. 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 9.4.2.

Record the name, start date (if known), indication for use and whether ongoing or stopped of medications/treatments taken within 2 weeks prior to informed consent and throughout 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.

9.4.2. Prohibited Medications

The drug classes listed in Appendix 1 are not permitted in the 14 days prior to the admission visit and for the duration of the study (up to the Day 28 visit). The list provides non-exhaustive examples of each drug class.

Subjects are not permitted to use alcohol, caffeine, or nicotine within 3 days prior to Admission visit through the Day 21 visit.

9.5. Treatment Compliance

Investigational product will be prepared by the site pharmacist. The Investigator(s) or designee will record the time and dose of study drug administration in the source documents. Any reasons for non-compliance will also be documented, including:

- Missed 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.

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 clinical Good Manufacturing Practice [GMP] conditions at [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.

10.2. Batch Formula for 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 by [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 (Kleptose®)	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

10.3. 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.

10.4. Study Drug Storage

Upon receipt of study drug (SAGE-217 and placebo), the Investigator or designee will inspect the medication 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 must be carefully stored at the temperature specified in the Pharmacy Manual (eg, clinical dosing solutions stored at approximately 2 to 8°C for 10 days or room temperature for up to 24 hours 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.

10.5. Administration and Study Drug Accountability

Doses will be prepared as an approximate 40 mL oral solution to be swallowed all at once, followed by approximately 200 mL of water which 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.

10.5.1. Study Drug Administration

While confined in the clinical unit (Day -1 through Day 3), subjects in Part A will receive a 10 mg dose of study drug administered in the morning on Day 1, 20 mg on Day 2, and 30 mg on Day 3.

While confined in the clinical unit in Part B (Day 7 through Day 10), subjects will receive randomized study drug in the morning and in the evening on Days 8, 9, and 10.

For non-confinement days (Days 4 through 6 [Part A] and Days 11 through 14 [Part B]), dosing will be done at the clinical site or, if suitable arrangements can be made, via home administration

where local regulations allow. Home administration of study drug will be performed according to a site-specific plan by a healthcare professional trained on the protocol and delivery of the study drug.

10.5.2. 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.

10.6. Study Drug Handling and Disposal

The pharmacist or designee for drug accountability is to document the date and time of initial compounding, subsequent admixture, administration of test article, 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 subject symptom response by a measurement of tremor amplitude, TETRAS upper limb subscale, and TETRAS Performance Subscale (items 4, 6, 7, and 8). Quality-of-life assessments include TETRAS ADL, QUEST, and video recording of subjects performing three everyday tasks. Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) and tremor oscillation as assessed by multidimensional accelerometer measurements (ie, raw accelerometer values) will be assessed by the Empatica Wristband E4.

11.1. Measurements of Tremor Amplitude

In order to measure essential tremor amplitude, subjects will wear a wireless ring motion sensor. The motion sensor measures linear acceleration and angular velocity (the Kinesia score). Amplitudes from the motion sensor data are collected for three upper limb maneuvers (postural tremor, wing beating, kinetic tremor) on each side of the body, for a total of six amplitude measures per assessment. Data are transmitted from the sensor to a computer using Bluetooth technology. Information from the motion sensor data correlates to symptoms of tremor. The Kinesia score ranges from 0 to 4 in 0.5 step increments. Higher scores indicate more tremors. The accelerometer assessment is completed in conjunction with the TETRAS Performance Subscale Item 4.

In Part A, Kinesia will be performed at screening and on Day -1 (Admission; three assessments separated by at least 30 minutes); a single assessment will be performed predose and 2, 12, and 14 hours postdose on Days 1, 2, and 7. In Part B, a single Kinesia reading will be performed before morning dose, after morning dose (2 hours post morning dose), before evening dose (12 hours post morning dose), and after evening dose (14 hours post morning dose) on Days 8, 9, and 14, and on Day 21.

11.2. TRG Essential Tremor Rating Assessment Scale (TETRAS) Performance Scale

Item #4 (upper limb tremor) of the TETRAS Performance Subscale will be completed using both the accelerometer and clinician assessment. Testing should be completed within ±10 minutes of the planned questionnaire time points. All three tests in the upper limb tremor series of assessments (Item 4) will be completed for both arms, first for the RIGHT arm and then for the LEFT. For each test, the maximum score is four, with a resulting maximum score of 24. Predose assessments can be done any time within 2 hours prior to the start of administration of solution. The Day 21 follow-up visit assessments can be done at any time during the visit. Subjects will complete the TETRAS Performance Subscale, Item #4 (upper limb tremor) while wearing the accelerometer. Simultaneous clinician assessment of Item #4 will occur. The accelerometer assessment is completed in conjunction with the TETRAS Performance Subscale at the same time points during the study.

In Part A, the TETRAS upper limb subscale will be performed at screening and on Day -1 (Admission; three assessments separated by at least 30 minutes); a single assessment of TETRAS upper limb subscale will be performed predose and 2, 12, and 14 hours postdose on

Days 1, 2, and 7. The TETRAS (all ADL and Performance Subscale [Items 4, 6, 7, and 8]) will be performed on Day -1 (Admission) and predose on Day 7. On days when the TETRAS all ADL and Performance Subscale are performed, Item # 4 will not be repeated.

In Part B, the TETRAS upper limb subscale will be before morning dose, after morning dose (2 hours post morning dose), before evening dose (12 hours post morning dose), and after evening dose (14 hours post morning dose) on Days 8, 9, and 14, and on Day 21. Item 4c (kinetic tremor) of the TETRAS upper limb subscale will be performed after morning dose (3 hours post morning dose) on Days 8 and 9. The TETRAS (all ADL and Performance Subscale [Items 4, 6, 7, and 8]) will be performed predose (morning and evening doses) on Day 14 and on Day 21. On days when the TETRAS all ADL and Performance Subscale are performed, Item # 4 will not be repeated.

Note that the bilateral TETRAS score for the test conducted during screening will be used to determine eligibility and must be ≥2 on each side (left and right) for kinetic tremor and ≥2 on each side (left and right) for either wing beating or forward outstretched postural tremor. A copy of the TETRAS is provided in Appendix 2.

11.3. Empatica Wristband E4

Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) will be assessed by the Empatica Wristband E4. The Empatica Wristband E4 is a wearable device that captures motion-based activity and sympathetic nervous system arousal. In Part A, the Empatica Wristband E4 will be worn during the Confinement Period. In Part B, the Empatica Wristband E4 will be worn during the Confinement Period and will be removed prior to discharge from the unit on Day 10. The Empatica device will be worn during the corresponding 3-hour postdose TETRAS upper limb subscale (Item 4c [kinetic tremor]) assessments. Data from the Empatica Wristband E4 will not be presented in the study report; instead, they will be part of a separate report.

11.4. Quality of Life in Essential Tremor Questionnaire (QUEST)

The QUEST is a brief, 30-item, ET-specific QOL scale in which subjects rate the extent to which tremor impacts a function or state, tremor severity in various body parts, perceived health, and overall QOL (Tröster 2005). The QUEST will be administered on Day -1 (Admission), Day 7, and on Day 14. A copy of the QUEST is provided in Appendix 3.

11.5. Video Recording

Videos of subjects performing three everyday tasks (drinking a glass of water, fastening a button, and one additional task that the subject experiences difficulty with on a daily basis) will be taken on Day -1 (Admission) and predose on Day 7 in Part A and predose (morning and evening doses) on Day 14 and on Day 21 in Part B.

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, 12, and 24 hours postdose on Day 1 and predose on Days 3, 4, 5, 6, and 7. In Part B, plasma samples for PK analysis will be collected 0.25, 0.5, 1, 2, 4, 8 (morning dose only), 12, and 24 hours postdose (morning and evening doses) on Day 8 and predose (morning and evening doses) on Days 10, 11, 12, 13, and 14. 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 CRF 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 SAGE-217 will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory.

13. ASSESSMENT OF SAFETY

13.1. Safety and Tolerability Parameters

Safety and tolerability of study drug will be evaluated by vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, SSS, MOAA/S scores, and adverse event reporting. The Bond-Lader Mood Rating Scale and a DEQ-5 will be used to assess mood and perception of drug effects, respectively.

13.1.1. Demographic/Medical History

Age, gender, race, and ethnic origin will be recorded at the Screening Visit. A full medical history including medication history will be recorded at the Screening Visit.

13.1.2. Vital Signs

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

In Part A, vital signs and pulse oximetry will be performed at screening (vital signs only) and Day -1 (Admission), predose on Day 1 and at 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours postdose on Days 1, 2, and 3, and predose on Days 5, 6, and 7. In Part B, for morning dose, vital signs (both supine for at least 5 minutes prior to the measurement and standing) and pulse oximetry will be performed predose on Day 8 and at 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours postdose on Days 8, 9, and 10, predose on Days 12, 13, and 14, and on Day 21. Vital signs and pulse oximetry assessments will be performed within ±10 minutes of the scheduled times through the 4-hour time point and within ±15 minutes of the scheduled times thereafter.

13.1.3. Weight and Height

Body weight and height will be measured at the Screening Visit.

13.1.4. Physical Examination

A physical examination of all major body systems will be undertaken and recorded at the Screening Visit.

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, predose on Day 1 and Day 7, and at 1 (±10 minutes), 12, and 24 (±15 minutes) hours postdose on Days 1, 2, 3, and 7. In Part B, the 12-lead ECG will be assessed at 1 (±10 minutes), 12, and 24 (±15 minutes) hours postdose on Days 8, 9, and 10, 1 (±10 minutes) and 12 (±15 minutes) hours post morning dose and 1 hour (±10 minutes) post evening dose on Day 14, and on Day 21.

All time points are relative to the time of dosing. ECGs will 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 and urine samples will be collected for hematology, serum chemistry, and urinalysis at the Screening Visit, on Day -1 (Admission), predose on Day 1, and predose on Day 2. In Part B, blood and urine samples will be collected predose (morning and evening doses) on Day 8, Day 9, and on Day 21.

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 13.2.1, and recorded in the eCRF.

13.1.6.1. Hematology

Hematology tests will include complete blood count, 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, AST, and ALT, total protein, and albumin.

Thyroid-stimulating hormone, thyroxine (T4), and triiodothyronine (T3) will be performed at screening to confirm subject eligibility.

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. Drugs Screen and Alcohol Test

A urine sample for assessment of selected drugs (sedative/hypnotics [eg, opioids], cotinine, and caffeine) and a breath sample for alcohol screen will be collected at screening and on Day -1. Results may be obtained through subject history. Subjects who use concomitant sedative/hypnotics will be excluded from the study. Use of alcohol, caffeine, or cotinine was not allowed for the duration of the study.

13.1.6.5. Virus Serology

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

13.1.6.6. Pregnancy Test

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at the Screening Visit and by urine pregnancy test on Day -1 (Admission), predose (morning dose) on Day 8, and at the follow-up visit on Day 28 in Part B.

13.1.6.7. Hormones and Exploratory Biochemistry

Optional blood samples will be collected at screening and on Days 3 and 7 and may be analyzed for stress hormone levels, kynurenine biochemistry, and markers of inflammation. Future research may suggest other biochemical markers as candidates for influencing not only response to SAGE-217 but also susceptibility to disorders for which SAGE-217 may be evaluated. Thus, the biochemical research may involve study of additional unnamed biochemical biomarkers, but only as related to disease susceptibility and drug action.

13.1.6.8. Genetic Testing

Where consent is given, an optional genetic sample for biomarker testing will be collected at the Screening Visit.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (ie, distribution, safety, tolerability, and efficacy) to SAGE-217. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (eg, cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of SAGE-217 (eg, AKR1C4 [3α-hydroxysteroid dehydrogenase]), genes associated with the γ-aminobutyric acid (GABA) receptor (eg, GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3), and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to **SAGE-217** but also susceptibility to disorders for which **SAGE-217** may be evaluated. Thus, the genetic research my involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

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 at screening (lifetime history and past 24 months). In Part A, the "Since Last Visit" C-SSRS form will be completed on Day -1 (Admission), 12 hours postdose on Day 1, predose on Day 4, and on Days 5, 6, and 7. In Part B, the "Since Last Visit" C-SSRS form will be completed 12 hours postdose (morning and evening

doses) on Day 8, predose (morning and evening doses) on Day 11, and on Days 12, 13, 14, 21, and 28. The C-SSRS is provided in Appendix 4.

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 predose on Day 1 and 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours postdose on Days 1, 2, and 3, and predose only on Days 5, 6, and 7. In Part B, the SSS will be administered predose (morning dose) on Day 8 and 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours postdose (morning dose) and 1, 3, 4, 6, and 8 hours postdose (evening dose) on Days 8, 9, and 10, predose (morning and evening doses) only on Days 12, 13, and 14, and on Day 21. 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 is provided in Appendix 5. The SSS should be performed prior to the MOAA/S score.

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 a MOAA/S score of 3 or less was observed, the score was to be confirmed by waiting approximately 10 minutes and re-administering the MOAA/S assessment. 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 on Day 1 and 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours postdose on Days 1, 2, and 3, predose only on Days 5, 6, and 7. In Part B, the MOAA/S will be performed predose (morning dose) on Day 8 and 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours postdose (morning dose) and 1, 3, 4, 6, and 8 hours postdose (evening dose) on Days 8, 9, and 10, predose (morning and evening doses) only on Days 12, 13, and 14, and on Day 21. The MOAA/S assessments will 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 24-hour time points. The MOAA/S is provided in Appendix 6.

13.1.10. Bond-Lader VAS Mood Scale

Mood will be assessed using the Bond-Lader Mood Rating Scale. This is a 16-part self-administered questionnaire that employs a 100-mm VAS to explore different aspects of self-reported mood. In Part A, the mood scale will be administered predose on Days 1, 2, and 7. In Part B, the mood scale will be administered predose (morning and evening doses) on Days 8, 9, 14 and 21. The Bond-Lader Mood Rating Scale is provided in Appendix 7.

13.1.11. Drug Effects Questionnaire (DEQ-5)

A DEQ-5 will be administered as follows:

1. Do you FEEL a drug effect right now?
2. Are you HIGH right now?

3. Do you DISLIKE any of the effects that you are feeling right now?
4. Do you LIKE any of the effects that you are feeling right now?
5. Would you like MORE of the drug you took, right now?

The answers are recorded on a 100-mm VAS, with the answer for each being "Not at all" and "Extremely" at the extremes. There will be options to record "Not applicable" for questions 3 and 4 if no drug effects are felt and for question 5 prior to administration of study medication. The DEQ-5 will be performed 2 hours postdose on Days 1 and 7 in Part A and 2 hours postdose (morning and evening doses) on Days 8 and 14 in Part B. The DEQ-5 is provided in Appendix 8.

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 causally 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.

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, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics or designee for the duration of the study (from the signing of the ICF through the Day 28 visit [or early termination]).

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 need not record sedation as an adverse event unless 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. 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, 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.

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. 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.
Probably 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. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

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 through the Day 28 visit (or early termination). 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)

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 28 visit (14 days following the last dose of study drug) or early termination. 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 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.

13.6. Emergency Identification of Study Drug (Part B)

Part B is a double-blind study. The pharmacist responsible for preparing the solutions will be unblinded and will retain an official paper copy of the randomization schedule.

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 eCRF. If the subject or study center personnel (other than pharmacist) have been unblinded, the subject will be terminated from the study.

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 complete at least one dose in Part B and have at least one post-randomization efficacy evaluation.

The evaluable population will consist of all randomized subjects with at least one post-randomization Kinesia assessment.

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

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, race, and ethnicity, and baseline characteristics, such as height, weight, and BMI, will be summarized.

Categorical summaries, such as race and ethnicity, 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, drug, 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. Primary Efficacy Endpoint

The change from randomization (predose on Day 8) in the accelerometer-based Kinesia kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) at Day 14 will be summarized by treatment group in Part B.

14.5. Secondary Efficacy Endpoints

The change from randomization (predose on Day 8) in the accelerometer-based Kinesia upper limb total and individual item scores, TETRAS total and individual upper limb item scores, and TETRAS Performance Subscale scores at Day 14 will be summarized by treatment group in Part B.

14.6. Exploratory Efficacy Endpoints

The change from randomization (predose on Day 8) in TETRAS ADL scores at Day 14 will be summarized by treatment group in Part B.

Empatica Wristband E4 Tremor oscillation and QUEST data will be listed by subject, study day, and time point.

A summary of clinical ratings of video recordings will be presented by group in Part B.

14.7. Safety and Tolerability Analyses

Data from vital signs, clinical laboratory measures, ECG, C-SSRS, and MOAA/S will be summarized using descriptive statistics by group and time point, where applicable. Continuous endpoints will be summarized with 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.

14.7.1. 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 and relationship to study drug (see Section 13.3).

TEAEs 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 signing of the ICF) through the Day 28 visit will be listed.

14.7.2. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from randomization in vital signs will be evaluated by time point.

14.7.3. Physical Examinations

Screening physical examination results will be listed by subject. Any clinically significant physical examination will be recorded in medical history.

14.7.4. 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.

14.7.5. Clinical Laboratory Evaluations

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline and randomization in clinical laboratory measures will be evaluated.

14.7.6. 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.

14.7.7. 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 Day 1 will be measured.

14.7.8. 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 Day 1 will be measured.

14.7.9. Bond-Lader VAS Mood Scale

Mood data collected on the Bond-Lader VAS mood scale will be listed by subject, study day, and time point. The scores and change from Day 1 will be summarized by study day and time point.

14.7.10. Drug Effects Questionnaire (DEQ-5)

Results from DEQ-5 will be listed by subject, study day, and time point. The result for each question and change from Day 1 will be summarized by study day and time point.

14.7.11. 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 within 2 weeks prior to the signing of the ICF. 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 part in which they are being taken. If a concomitant medication assigned to a 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.

14.8. Pharmacokinetic Analysis

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics. Time to reach maximum concentration (t_{max}) will be summarized using 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.

Pharmacokinetic and pharmacodynamic modelling assessment of the relationship between plasma exposure of SAGE-217 and change from baseline in accelerometer-based Kinesia scores may be assessed.

14.9. Determination of Sample Size

Up to 80 subjects will be enrolled in Part A to yield at least 60 randomized subjects for Part B. A total sample size of 51 evaluable subjects (ie, 17 per group) will have 80% power to detect a difference in means of 3.0 on the primary endpoint assuming that the common standard deviation is 3.0 using a 2-group t-test with a 0.05 two-sided significance level. Assuming a 15% non-evaluability rate, 20 subjects per group will be randomized. The number of subjects in each treatment group is also thought to be sufficient to assess preliminary safety and tolerability following multiple doses of SAGE-217 Oral Solution.

14.10. 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 subject into the study, a representative of Sage Therapeutics or designee will visit the investigational study site to:

- Determine the adequacy of the facilities; and
- 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 CRFs, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject'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 subject (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 CRFs 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 subject 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 CRFs.

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 CRFs 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 trial 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.

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21. APPENDICES

Copies of scales and questionnaires included in Appendix 2 through Appendix 8 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. TREMOROGENIC DRUGS

The following drug classes are not permitted in the 14 days prior to the admission visit and for the duration of the study (up to the Day 21 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
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
Statins
atorvastatin

Sympathomimetics
epinephrine, pseudoephedrine
Weight loss medication
tiratricol
Xanthine derivatives
theophylline

APPENDIX 2. TRG ESSENTIAL TREMOR RATING ASSESSMENT SCALE (TETRAS)

TRG ESSENTIAL TREMOR RATING ASSESSMENT SCALE (TETRAS©) V 3.1

Activities of Daily Living Subscale

Rate tremor's impact on activities of daily living (0 - 4 scoring).

1. Speaking
0 = Normal.
1 = Slight voice tremulousness, only when "nervous".
2 = Mild voice tremor. All words easily understood.
3 = Moderate voice tremor. Some words difficult to understand.
4 = Severe voice tremor. Most words difficult to understand.

2. Feeding with a spoon
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with feeding with a spoon.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot feed with a spoon.

3. Drinking from a glass
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with drinking from a glass.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.

4. Hygiene
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with hygiene.
2 = Mildly abnormal. Some difficulty but can complete task.
3 = Moderately abnormal. Unable to do most fine tasks such as putting on lipstick or shaving unless changes strategy such as using two hands or using the less affected hand.
4 = Severely abnormal. Cannot complete hygiene activities independently.

5. Dressing
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with dressing.
2 = Mildly abnormal. Able to do everything but has difficulty due to tremor.
3 = Moderately abnormal. Unable to do most dressing unless uses strategy such as using Velcro, buttoning shirt before putting it on or avoiding shoes with laces.
4 = Severely abnormal. Cannot dress independently.

6. Pouring
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with pouring.
2 = Mildly abnormal. Must be very careful to avoid spilling but may spill occasionally.
3 = Moderately abnormal. Must use two hands or uses other strategies to avoid spilling.
4 = Severely abnormal. Cannot pour.

7. Carrying food trays, plates or similar items
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with carrying food trays, plates or similar items.
2 = Mildly abnormal. Must be very careful to avoid spilling items on food tray.
3 = Moderately abnormal. Uses strategies such as holding tightly against body to carry.
4 = Severely abnormal. Cannot carry food trays or similar items.

8. Using Keys
0 = Normal
1 = Slightly abnormal. Tremor is present but can insert key with one hand without difficulty.
2 = Mildly abnormal. Commonly misses target but still routinely puts key in lock with one hand.
3 = Moderately abnormal. Needs to use two hands or other strategies to put key in lock.
4 = Severely abnormal. Cannot put key in lock.

9. Writing
0 = Normal
1 = Slightly abnormal. Tremor present but does not interfere with writing.
2 = Mildly abnormal. Difficulty writing due to the tremor
3 = Moderately abnormal. Cannot write without using strategies such as holding the writing hand with the other hand, holding pen differently or using large pen.
4 = Severely abnormal. Cannot write.

10. Working. If patient is retired, ask as if they were still working. If the patient is a housewife, ask the question as it relates to housework:
0 = Normal .
1 = Slightly abnormal. Tremor is present but does not affect performance at work or at home.
2 = Mildly abnormal. Tremor interferes with work; able to do everything, but with errors. .
3 = Moderately abnormal. Unable to continue working without using strategies such as changing jobs or using special equipment.
4 = Severely abnormal. Cannot perform any job or household work.

11. Overall disability with the most affected task (Name task, e.g. using computer mouse, writi etc)

Task _____

0 = Normal.
1 = Slightly abnormal. Tremor present but does not affect task.
2 = Mildly abnormal. Tremor interferes with task but is still able to perform task.
3 = Moderately abnormal. Can do task but must use strategies.
4 = Severely abnormal. Cannot do the task.

12. Social Impact

0 = None
1 = Aware of tremor, but it does not affect lifestyle or professional life.
2 = Feels embarrassed by tremor in some social situations or professional meetings.
3 = Avoids participating in some social situations or professional meetings because of tremor.
4 = Avoids participating in most social situations or professional meetings because of tremor.

Performance Subscale

Instructions

Scoring is 0 – 4. For most items, the scores are defined only by whole numbers, but 0.5 increments may be used if you believe the rating is between two whole number ratings and cannot be reconciled to a whole number. Each 0.5 increment in rating is specifically defined for the assessment of upper limb postural and kinetic tremor and the dot approximation task (items 4 and 8). All items of the examination, except standing tremor, are performed with the patient seated comfortably. For each item, score the highest amplitude seen at any point during the exam. Instruct patients not to attempt to suppress the tremor, but to let it come out.

1. Head tremor: The head is rotated fully left and right and then observed for 10s in mid position. Patient then is instructed to gaze fully to the left and then to the right with the head in mid position. The nose should be used as the landmark to assess and rate the largest amplitude excursions during the examination.

   0 = no tremor
   1 = slight tremor (< 0.5 cm)
   2 = mild tremor (0.5- < 2.5 cm)
   3 = moderate tremor (2.5-5 cm)
   4 = severe or disfiguring tremor (> 5 cm)

2. Face (including jaw) tremor: Smile, close eyes, open mouth, purse lips. The highest amplitude of the most involved facial anatomy is scored, regardless of whether it occurs during rest or activation. Repetitive blinking or eye fluttering should not be considered as part of facial tremor.

   0 = no tremor
   1 = slight; barely perceptible tremor
   2 = mild: noticeable tremor
   3 = moderate: obvious tremor, present in most voluntary facial contractions
   4 = severe: gross disfiguring tremor

3. Voice tremor: First ask subject to produce an extended "aaah" sound and eee" sound for 5 seconds each. Then assess speech during normal conversation by asking patients "How do you spend your average day?".

   0 = no tremor
   1 = slight: tremor during aaah, and eee and no tremor during speech
   2 = mild: tremor in "aaah" and "eee" and minimal tremor in speech
   3 = moderate: obvious tremor in speech that is fully intelligible
   4 = severe: some words difficult to understand

4. Upper limb tremor: Tremor is assessed during three maneuvers: forward horizontal reach posture, lateral "wing beating" posture and finger-nose-finger testing. Each upper limb is assessed and scored individually. The forward horizontal reach posture is held for 5 seconds.

The lateral wing beating posture is held for 20 seconds. The finger-nose-finger movement is executed three times. Amplitude assessment should be estimated using the maximally displaced point of the hand at the point of greatest displacement along any single plane. For example, the amplitude of a pure supination-pronation tremor, pivoting around the wrist would be assessed at either the thumb or fifth digit.

a. Forward outstretched postural tremor: Subjects should bring their arms forward, slightly lateral to midline and parallel to the ground. The wrist should also be straight and the fingers abducted so that they do not touch each other.
b. Lateral "wing beating" postural tremor: Subjects will abduct their arms parallel to the ground and flex the elbows so that the two hands do not quite touch each other and are at the level of the nose. The fingers are abducted so that they do not touch each other. The posture should be held for 20 seconds.
c. Kinetic tremor: Subjects extend only their index finger. They then touch a set object or the examiners finger located to the full extent of their reach, which is located at the same height (parallel to the ground) and slightly lateral to the midline. Subjects then touch their own nose (or chin if the tremor is severe) and repeat this back and forth three times. Only the position along the trajectory of greatest tremor amplitude is assessed. This will typically be either at the nose or at the point of full limb extension.

For all three hand tremor ratings

0 = no tremor
1 = tremor is barely visible
1.5 = tremor is visible, but less than 1 cm
2 = tremor is 1- < 3 cm amplitude
2.5 = tremor is 3- < 5 cm amplitude
3 = tremor is 5- < 10 cm amplitude
3.5 = tremor is 10- < 20 cm amplitude
4 = tremor is $\geq$ 20 cm amplitude

5. Lower limb tremor: Raise each lower limb horizontally parallel to the ground for 5 seconds each. Then perform a standard heel to shin maneuver with each leg, three times. The maximum tremor in either maneuver is scored, and only the limb with the largest tremor is scored. Tremor may exist in any part of the limb, including foot.

0 = no tremor
1 = slight: barely perceptible
2 = mild, less than 1 cm at any point
3 = moderate tremor, less than 5 cm at any point
4 = severe tremor, greater than 5 cm

6. Archimedes spirals: Demonstrate how to draw Archimedes spiral that approximately fills ¼ of an unlined page of standard (letter) paper. The lines of the spiral should be approximately 1.3 cm (0.5 inch) apart. Then ask the subject to copy the spiral. Test and score each hand separately. Use a ballpoint pen. The pen should be held such that no part of the limb touches the table. Secure the paper on the table in a location that is suitable for the patient's style of drawing. Score the tremor in the spiral, not the movement of the limb.

   0 = normal
   1 = slight: tremor barely visible.
   2 = mild: obvious tremor
   3 = moderate: portions of figure not recognizable.
   4 = severe: figure not recognizable

7. Handwriting: Have patient write the standard sentence "This is a sample of my best handwriting" using the dominant hand only. Patients must write cursively (i.e., no printing). They cannot hold or stabilize their hand with the other hand.. Use a ballpoint pen. Secure the paper on the table in a location that is suitable for the patient's style of writing. Score the tremor in the writing, not the movement of the limb.

   0 = normal
   1 = slight: untidy due to tremor that is barely visible.
   2 = mild: legible, but with considerable tremor.
   3 = moderate: some words illegible.
   4 = severe: completely illegible

8. Dot approximation task: The examiner makes a dot or X and instructs the subject to hold the tip of the pen "as close as possible to the dot (or center of an X) without touching it, (ideally approximately 1 mm) for 10 seconds ". Each hand is score separately.

   0 = no tremor
   1 = tremor is barely visible
   1.5 = tremor is visible, but less than 1 cm
   2 = tremor is 1- < 3 cm amplitude
   2.5 = tremor is 3- < 5 cm amplitude
   3 = tremor is 5- < 10 cm amplitude
   3.5 = tremor is 10- < 20 cm amplitude
   4 = tremor is $\geq$ 20 cm amplitude

9. Standing tremor: Subjects are standing, unaided if possible. The knees are 10-20 cm apart and are flexed 10-20°. The arms are down at the subject's side. Tremor is assessed at any point on the legs or trunk
   0 = no tremor
   1 = barely perceptible tremor
   2 = obvious but mild tremor, does not cause instability
   3 = moderate tremor, impairs stability of stance
   4 = severe tremor, unable to stand without assistance

Appendix 3. QUALITY OF LIFE IN ESSENTIAL TREMOR QUESTIONNAIRE (QUEST)

Quality of Life in Essential Tremor Questionnaire (QUEST)

Patient's Name: _____ ID: _____ Date: ____/____/____

Gender: ☐ Male ☐ Female Date of Birth: ____/____/____

Heath Status

In general, how would you rate your overall health? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

Overall Quality of Life

Overall, how would you rate your quality of life? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

General Information

In the past month, has your tremor interfered with your sexual satisfaction?	**Y**	**N**
In the past month, have you had side effects from tremor medications?	Y	N
In the past month, have you been satisfied with the tremor control achieved by your medications?	**Y**	**N**

Which most appropriately describes your work status?

- ☐ Never worked
- ☐ Not working, retired because of tremor
- ☐ Not working, retired NOT due to tremor
- ☐ Working full time
- ☐ Working part time

TREMOR SELF ASSESSMENT

For the purposes of this questionnaire, tremor is defined as uncontrollable shaking or quivering of the body part in question.

On a typical day, how many of your waking hours do you have tremor in ANY body part?

Circle: 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Put a mark in the box to rate the severity of your tremor in each of the body parts listed below.

None - no tremor at any time
Mild - mild tremor not causing difficulty in performing any activities
Moderate - tremor causes difficulty in performing **some** activities
Marked - tremor causes difficulty in performing **most** or **all** activities
Severe - tremor **prevents** performing some activities

		None	Mild	Moderate	Marked	Severe
1.	**Head**	☐	☐	☐	☐	☐
2.	Voice	☐	☐	☐	☐	☐
3.	**Right arm/hand**	☐	☐	☐	☐	☐
4.	Left arm/hand	☐	☐	☐	☐	☐
5.	**Right leg/foot**	☐	☐	☐	☐	☐
6.	Left leg/foot	☐	☐	☐	☐	☐

continued on next page

For each question below, please mark the box which best describes your current situation.

For example: N R ~~S~~ F A

N = Never/No
R = Rarely
S = Sometimes
F = Frequently
A = Always/Yes
NA = Not Applicable

1.	My tremor interferes with my ability to communicate with others.		N	R	S	F	A
2.	My tremor interferes with my ability to maintain conversations with others.		N	R	S	F	A
3.	It is difficult for others to understand my speech because of my tremor.		N	R	S	F	A
4.	My tremor interferes with my job or profession.	NA	N	R	S	F	A
5.	I have had to change jobs because of my tremor.	NA	N	R	S	F	A
6.	I had to retire or take early retirement because of my tremor.		N				A
7.	I am only working part time because of my tremor.	NA	N				A
8.	I have had to use special aids or accommodations in order to continue my job due to my tremor.	NA	N	R	S	F	A
9.	My tremor has led to financial problems or concerns.		N	R	S	F	A
10.	I have lost interest in my hobbies because of my tremor.		N	R	S	F	A
11.	I have quit some of my hobbies because of my tremor.		N				A
12.	I have had to change or develop new hobbies because of my tremor.		N				A
13.	My tremor interferes with my ability to write (for example, writing letters, completing forms).		N	R	S	F	A
14.	My tremor interferes with my ability to use a typewriter or computer.	NA	N	R	S	F	A
15.	My tremor interferes with my ability to use the telephone (for example, dialing, holding the phone).		N	R	S	F	A
16.	My tremor interferes with my ability to fix small things around the house (for example, change light bulbs, minor plumbing, fixing household appliances, fixing broken items).		N	R	S	F	A
17.	My tremor interferes with dressing (for example, buttoning, zipping, tying shoes).		N	R	S	F	A
18.	My tremor interferes with brushing or flossing my teeth.		N	R	S	F	A
19.	My tremor interferes with eating (for example, bringing food to mouth, spilling).		N	R	S	F	A
20.	My tremor interferes with drinking liquids (for example, bringing to mouth, spilling, pouring).		N	R	S	F	A
21.	My tremor interferes with reading or holding reading material.		N	R	S	F	A
22.	My tremor interferes with my relationships with others (for example, my family, friends, coworkers).		N	R	S	F	A
23.	My tremor makes me feel negative about myself.		N	R	S	F	A
24.	I am embarrassed about my tremor.		N	R	S	F	A
25.	I am depressed because of my tremor.		N	R	S	F	A
26.	I feel isolated or lonely because of my tremor.		N	R	S	F	A
27.	I worry about the future due to my tremor.		N	R	S	F	A
28.	I am nervous or anxious.		N	R	S	F	A
29.	I use alcohol more frequently than I would like to because of my tremor.		N	R	S	F	A
30.	I have difficulty concentrating because of my tremor.		N	R	S	F	A

THANK YOU!

APPENDIX 4. COLUMBIA – SUICIDE SEVERITY RATING SCALE (C-SSRS)

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

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 5. STANFORD SLEEPINESS SCALE (SSS)

Stanford Sleepiness Scale

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

Table 1. 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

APPENDIX 7. BOND-LADER VAS (MOOD RATING SCALE)

1. Please rate the way you feel in terms of the dimensions given below.
2. Regard the line as representing the full range of each dimension.
3. Rate your feelings as they are at the moment.
4. Mark clearly and perpendicularly across each line.

Alert	_____	Drowsy
Calm	_____	Excited
Strong	_____	Feeble
Muzzy	_____	Clear-headed
Well-coordinated	_____	Clumsy
Lethargic	_____	Energetic
Contented	_____	Discontented
Troubled	_____	Tranquil
Mentally slow	_____	Quick-witted
Tense	_____	Relaxed
Attentive	_____	Dreamy
Incompetent	_____	Proficient
Happy	_____	Sad
Antagonistic	_____	Amicable
Interested	_____	Bored
Withdrawn	_____	Gregarious

APPENDIX 8. DRUG EFFECTS QUESTIONNAIRE (DEQ-5)

Instructions: This questionnaire asks about how you are feeling after taking the substance that was given to you. Please draw a mark on the line to show how strongly you are feeling each of the following effects ***right now***. You can mark anywhere on the line, but please draw a vertical line (one that goes straight up and down).

Let's look at an example first.

EXAMPLE: Do you feel dizzy right now?
If you do not feel dizzy, draw a line at NOT AT ALL. If you feel very dizzy, draw a line at EXTREMELY. If you feel somewhere in between, you can draw a mark anywhere along the line between NOT AT ALL and EXTREMELY to indicate how dizzy you are. For example, if you feel a little dizzy, you might draw a line that looks something like the example below.

1. Do you FEEL a drug effect right now?

2. Are you HIGH right now?

3. Do you DISLIKE any of the effects you are feeling right now?

4. Do you LIKE any of the effects you are feeling right now?

5. Would you like MORE of the drug you took, right now?

1. TITLE PAGE

PROTOCOL NUMBER: 217-ETD-201

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

IND NUMBER: 131,258

Investigational Product	SAGE-217
Clinical Phase	2a
Sponsor	Sage Therapeutics, Inc.
Sponsor Contact	[redacted], M.S.H.S. [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	19 August 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.

PROTOCOL SIGNATURE PAGE

Protocol Number:	217-ETD-201
Product:	SAGE-217 Oral Solution
IND No.:	131,258
Study Phase:	2a
Sponsor:	Sage Therapeutics
Date of Original Protocol:	Version 1.0 19 August 2016

Sponsor Approval

[redacted]

22 August 2016

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

Date (DD/MMM/YYYY)

[redacted]

22 August 2016

[redacted], PharmD, M.S., R.Ph.
Sage Therapeutics

Date (DD/MMM/YYYY)

[redacted]

23 Aug 2016

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

Date (DD/MMM/YYYY)

[redacted]

23 AUG 2016

[redacted], M.S.
Statistician
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-ETD-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
Sponsor Physician	[redacted], M.D., M.P.H. Sage Therapeutics	215 First Street, Suite 220 Cambridge, MA 02142 Cell: [redacted]
Sponsor Signatory	[redacted], M.D., Ph.D.	215 First Street, Suite 220 Cambridge, MA 02142 Office: [redacted] Cell: [redacted]
Medical Monitor	[redacted], M.D.	[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 2a, Double-Blind, Placebo-Controlled, Randomized Withdrawal Study Evaluating the Efficacy, Safety, Tolerability, and Pharmacokinetics of SAGE-217 Oral Solution in the Treatment of Subjects with Essential Tremor (ET)

Study center(s): Up to 30 centers

Phase of development: 2a

Methodology:

This study will assess the efficacy, safety, tolerability, and PK of SAGE-217 Oral Solution.

There are two parts:

Part A: Open-label with morning dosing (7 days).

All subjects will start on a 10 mg dose of study drug administered with food in the morning on Day 1. Subjects will receive 20 mg with food on Day 2 and 30 mg with food daily on Days 3 to 7.

Part B: Double-blind, placebo-controlled, randomized withdrawal with morning and evening dosing (7 days).

In order to qualify for Part B of the study, a subject must tolerate a maximum dose of at least 10 mg of SAGE-217, and the subject must have responded to SAGE-217, defined as a 30% reduction from baseline in the TRG Essential Tremor Rating Assessment Scale (TETRAS) kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) on Day 7.

Eligible subjects will be randomized in a 1:1:1 fashion to SAGE-217 morning dosing, SAGE-217 evening dosing, or placebo. In order to preserve the blind, those randomized to SAGE-217 morning dosing will receive placebo for the evening dose, those randomized to SAGE-217 evening dosing will receive placebo for the morning dose, and those randomized to placebo will receive placebo for both morning and evening dosing. Subjects randomized to SAGE-217 will receive their maximum dose as determined in Part A. Subjects randomized to the placebo arm will represent randomized withdrawal (withdrawal from treatment they received in Part A). Subjects will be administered study drug with meals in the morning and in the evening for 7 consecutive days.

Methodology:

Dose adjustments will only be allowed during the open-label phase of the study (Part A). If at any time the dose is not tolerated in Part A, assessed by occurrence of a severe adverse event judged by the investigator to be related to study drug, the dose on the next day will be reduced to the next lowest dose and continued for the remainder of the open-label dosing period (ie, subjects who are unable to tolerate the 30 mg dose will receive a lower dose of 20 mg, and subjects who are unable to tolerate 20 mg will be given a 10 mg dose). The dose tolerated for Days 5, 6, and 7 of the open-label dosing period will be determined to be the maximum dose for that subject. Subjects who require dose adjustments on Days 5, 6, and 7 of Part A will not progress to Part B.

Subjects will be exposed to study drug (SAGE-217 or placebo) for up to 14 days and will be followed for an additional 14 days after the administration of the last dose.

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

Objectives:

Primary:

- The primary objective of this study is to compare the effect of 7 days administration of SAGE-217 Oral Solution to placebo on the change in tremor severity.

Secondary:

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

- Tremor severity, as assessed by the change from randomization (Day 8) in the accelerometer-based Kinesia upper limb total score (ie, the sum of forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores across both sides of the body) and individual item scores at Day 14.
- Tremor severity, as measured by the change from randomization (Day 8) in the TETRAS upper limb total score (ie, the sum of item 4c scores from both sides of the body) and individual TETRAS upper limb item scores at Day 14.
- Tremor severity, as assessed by the change from randomization (Day 8) in TETRAS Performance Subscale scores measured at Day 14.
- Safety and tolerability, as assessed by vital signs measurements, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse event reporting.
- Sleepiness/sedation, as assessed by the Stanford Sleepiness Scale (SSS) and Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scores.
- Mood, as assessed by the Bond-Lader visual analogue scale (VAS) Mood Scale scores.
- How the subject feels after taking the study drug as assessed by Drug Effects Questionnaire (DEQ-5) ratings.

In addition, plasma concentrations of SAGE-217 and SAGE-217 metabolites may be measured. Pharmacokinetic (PK) parameters, such as area under the concentration-time curve from time zero to last time point (AUC_{0-t}), 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}), and terminal half-life ($t_{1/2}$), will be derived, where appropriate.

Exploratory:

The exploratory objectives of the study are to compare the effect of 7 days administration of SAGE-217 Oral Solution to placebo on:

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

In addition, PK/pharmacodynamics (PD) modelling assessment of the relationship between plasma exposure of SAGE-217 and change from baseline in accelerometer-based Kinesia scores.

Endpoints:

The primary endpoint of this study is the change from randomization (Day 8) in the accelerometer-based Kinesia kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) at Day 14.

Number of subjects (planned):

Up to 80 subjects will be enrolled in Part A to yield at least 60 randomized subjects for Part B.

Diagnosis and main criteria for inclusion:

Inclusion criteria:

1. Subject has signed an informed consent form before any study-specific procedures are performed.
2. Subject must be between 18 and 75 years of age, inclusive.
3. Subject must have a diagnosis of ET, defined as bilateral postural tremor and kinetic tremor, involving hands and forearms, that is visible and persistent and the duration is >5 years prior to screening.
4. Subject must have bilateral TETRAS scores of at least two on each side (left and right) for kinetic tremor and at least two on each side (left and right) for either wing beating or forward outstretched postural tremor.
5. Subject must be willing to discontinue medications taken for the treatment of ET, alcohol, nicotine, and caffeine through Day 21 of the study.
6. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests.
7. Female subjects must be post-menopausal, permanently sterile (bilateral tubal occlusion), or of childbearing potential with a negative pregnancy test, non- breastfeeding, and using two highly effective methods of birth control prior to screening, throughout study participation and for 14 days after the last dose of study drug (as defined in Section 8.1).
8. 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.
9. Males must be willing to abstain from sperm donation while on study through 13 weeks after receiving the last dose of study drug.

Exclusion criteria:

1. Subject has presence of abnormal neurological signs other than tremor or Froment's sign.
2. Subject has presence of known causes of enhanced physiological tremor.
3. Subject has concurrent or recent exposure (14 days prior to admission visit) to tremorogenic drugs, as defined in Appendix 1, or the presence of a drug withdrawal state.
4. Subject has had direct or indirect trauma to the nervous system within 3 months before the onset of tremor.
5. Subject has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.).
6. Subject has convincing evidence of sudden tremor onset or evidence of stepwise deterioration of tremor.
7. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.
8. Subject has clinically significant abnormal physical examination or 12-lead ECG at the Screening or Admission Visits. Note: A 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. An ECG may be repeated if initial values obtained exceed the limits specified.
9. Subject has a history, presence, and/or current evidence of serologic positive results for hepatitis B surface antigen, hepatitis C antibodies, or human immunodeficiency virus 1 or 2 antibodies.
10. Subject has hyperthyroidism.
11. Subject has used alcohol, caffeine, or nicotine within 3 days prior to Admission visit.
12. Subject has a known allergy to SAGE-217 and its major excipient hydroxylpropyl-β-cyclodextrin (HPβCD).
13. Subject has exposure to another investigational medication or device within the prior 30 days.
14. Subject has a history of suicidal behavior within 2 years or answers "YES" to questions 3, 4, or 5 on the C-SSRS at the Screening Visit or on Day -1 or is currently at risk of suicide in the opinion of the Investigator.
15. Subject has donated one or more units (1 unit = 450 mL) of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing.
16. Subject is unwilling or unable to comply with study procedures.
17. Use of 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:

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:

Screening Duration: approximately 28 days; Treatment Period: 14 days; Follow-up: 14 days

Planned Study Duration per Subject: approximately 56 days

Reference therapy, dosage and mode of administration:

Placebo will be matched to study drug in Part B.

Criteria for evaluation:

Efficacy:

Transducer measurement of tremor amplitude using an accelerometer and TETRAS Performance Subscale. Quality-of-life will be evaluated using the TETRAS ADL, QUEST, and video recording of subjects performing three everyday tasks. Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) will be assessed by the Empatica Wristband E4.

Pharmacokinetics:

Plasma will be collected to assay for concentrations of SAGE-217 and may be assayed for SAGE-217 metabolites, if deemed necessary. The following PK parameters will be derived from the plasma concentrations (where evaluable): $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, and $t_{½}$.

Safety and Tolerability:

Safety and tolerability of study drug will be evaluated by vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, SSS, MOAA/S scores, and adverse event reporting. The Bond-Lader Mood Rating Scale and a DEQ-5 will be used to assess mood and perception of drug effects, respectively.

Statistical methods:

Study Populations

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 complete at least one dose in Part B and have at least one post-randomization efficacy evaluation.

The evaluable population will consist of all randomized subjects with at least one post-randomization Kinesia assessment.

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

Efficacy Analysis

Efficacy data (including change from randomization values for accelerometer-derived Kinesia and clinician-rated TETRAS scores) will be summarized using appropriate descriptive statistics and listed by subject.

The change from randomization (Day 8) in the accelerometer-based Kinesia kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) at Day 14 will be summarized by treatment. Additionally, the change from randomization in the accelerometer-based Kinesia upper limb total score and individual item scores at Day 14 will be summarized by treatment.

The change from randomization in TETRAS upper limb total score, individual TETRAS upper limb item scores, and TETRAS Performance Subscale scores at Day 14 will be summarized by treatment.

Pharmacokinetic Analysis

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics and listed by subject. Wherever necessary and appropriate, PK parameters will be dose-adjusted to account for individual differences in dose.

Safety Analysis

Adverse events will be coded using Medical Dictionary for Regulatory Activities™. The overall incidence of adverse events will be displayed by System Organ Class, preferred term, and dose group. Incidence of adverse events will also be presented by maximum severity and relationship to study drug. Data from vital signs, clinical laboratory measures, ECG, and C-SSRS will be summarized using descriptive statistics by dose group, where applicable. Continuous endpoints will be summarized with 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 the same summary 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.

Sample Size

Up to 80 subjects will be enrolled in Part A to yield at least 60 randomized subjects for Part B. A total sample size of 51 evaluable subjects (ie, 17 per group) will have 80% power to detect a difference in means of 3.0 on the primary endpoint assuming that the common standard deviation is 3.0 using a 2-group t-test with a 0.05 two-sided significance level. Assuming a 15% non-evaluability rate, 20 subjects per group will be randomized. The number of subjects in each treatment group is also thought to be sufficient to assess preliminary safety and tolerability following multiple doses of SAGE-217 Oral Solution.

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

Visit Days	Screening (Day -28 to Day -1)	Admit (Day -1)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Informed consent	X								
Inclusion/exclusion	X	X							
Confined to unit		X	X	X	X				X
Demographics	X								
Medical history	X								
Physical examination	X								
Body weight/height	X								
Complete blood count/ serum chemistry[a]	X	X	X	X					
Pregnancy test	X (serum)	X (urine)							
Urinalysis[a]	X	X	X	X					
Hepatitis & HIV screen	X								
Vital signs[b]	X	X	X	X	X	X	X	X	X
Pulse oximetry[b]		X	X	X	X	X	X	X	X
12-lead ECG[c]	X		X	X	X				X
C-SSRS[d]		X	X			X	X	X	X
SSS[e]			X	X	X	X	X	X	X
MOAA/S[f]			X	X	X	X	X	X	X
Bond-Lader-VAS[g]			X	X					X
DEQ-5[h]			X						X
Kinesia (accelerometer)[i]		X	X	X					X
TETRAS upper limb subscale[i]	X	X	X	X					X

Visit Days	Screening (Day -28 to Day -1)	Admit (Day -1)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
TETRAS (all ADL and all Performance Subscale)[j]		X							X
Empatica Wristband E4[k]		X	X	X	X				X
QUEST		X							X
Plasma PK samples[l]			X	X	X	X	X	X	X
Administer study drug[m]			X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
Videos[n]		X							X

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

[a] Screening and safety laboratory tests will be performed at Screening, Day -1 (Admission), Day 1, and predose on Day 2.

[b] Vital signs (both supine for at least 5 minutes prior to the measurement and standing) and pulse oximetry will be performed at Screening (vital signs only) and Day -1 (Admission), predose and at 1, 2, 3, 4, 6, 8, 12, 14, 16, and 24 hours postdose on Days 1, 2, and 3, and predose only on Days 4, 5, 6, and 7.

[c] 12-lead ECGs will be performed at Screening, predose on Day 1, and at 1, 12, and 24 hours postdose on Days 1, 2, 3, and 7.

[d] The C-SSRS will be performed on Day -1 (Admission), 12 hours postdose on Day 1, predose on Day 4, and on Days 5, 6, and 7.

[e] The SSS will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, 16, and 24 hours postdose on Days 1, 2, and 3, and predose only on Days 4, 5, 6, and 7.

[f] The MOAA/S will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, 16, and 24 hours postdose on Days 1, 2, and 3, and predose only on Days 4, 5, 6, and 7.

[g] The Bond-Lader VAS will be at performed predose on Days 1, 2, and 7.

[h] The DEQ-5 will be performed 2 hours postdose on Days 1 and 7.

[i] Kinesia and TETRAS upper limb subscale will be performed at Screening (TETRAS upper limb subscale only), predose on Day -1 (Admission; three assessments separated by at least 30 minutes), and predose and 2, 12, and 14 hours postdose (three assessments separated by at least 30 minutes) on Days 1, 2, and 7.

[j] TETRAS (all ADL) will be performed on Day -1 (Admission) and Day 7.

[k] The Empatica Wristband E4 will be worn during the Confinement Periods.

[l] Plasma pharmacokinetic samples will be taken predose and 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours postdose on Day 1 and predose on Days 2, 3, 4, 5, 6, and 7.

[m] Study drug will be administered in the morning with food during Part A.

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

Table 3: Schedule of Events: Part B (Randomized Withdrawal)

Visit Days	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Follow-up Day 21	End of Study Day 28
Randomization	X								
Confined to unit	X	X	X						
Complete blood count/ serum chemistry[a]	X	X						X	
Pregnancy test									X
Urinalysis[a]	X	X						X	
Vital signs[b]	X	X	X	X	X	X	X	X	
Pulse oximetry[b]	X	X	X	X	X	X	X	X	
12-lead ECG[c]	X	X	X				X	X	
C-SSRS[d]	X			X	X	X	X	X	X
SSS[e]	X	X	X	X	X	X	X	X	
MOAA/S[f]	X	X	X	X	X	X	X	X	
Bond-Lader-VAS[g]	X	X					X	X	
DEQ-5[h]	X						X		
Kinesia (accelerometer)[i]	X	X					X	X	
TETRAS upper limb subscale[i]	X	X					X	X	
TETRAS (all ADL and all Performance Subscale)[j]							X	X	
Empatica Wristband E4[k]	X	X	X				X		
QUEST							X		
Plasma PK samples[l]	X	X	X	X	X	X	X		
Administer study drug[m]	X	X	X	X	X	X	X		

Visit Days	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Follow-up Day 21	End of Study Day 28
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Videos[n]							X	X	

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

[a] Safety laboratory tests will be performed predose on Day 8, Day 9, and on Day 21.

[b] Vital signs (both supine for at least 5 minutes prior to the measurement and standing) and pulse oximetry will be performed predose and at 1, 2, 3, 4, 6, 8, 12, 14, 16, and 24 hours postdose on Days 8, 9, and 10, predose only on Days 11, 12, 13, and 14, and on Day 21.

[c] 12-lead ECGs will be performed at 1, 12, and 24 hours postdose on Days 8, 9, and 10, on Day 14, and Day 21.

[d] The C-SSRS will be performed on Days 8, 11, 12, 13, and 14, on Day 21, and on Day 28.

[e] The SSS will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, 16, and 24 hours postdose on Days 8, 9, and 10, predose only on Days 11, 12, 13, and 14, and on Day 21.

[f] The MOAA/S will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, 16, and 24 hours postdose on Days 8, 9, and 10, predose only on Days 11, 12, 13, and 14, and on Day 21.

[g] The Bond-Lader VAS will be at performed predose on Days 8, 9, and 14 and on Day 21.

[h] The DEQ-5 will be performed 2 hours postdose on Days 8 and 14.

[i] Kinesia and TETRAS upper limb subscale will be performed before morning dose, after morning dose (2 hours post morning dose), before evening dose (12 hours post morning dose), and after evening dose (14 hours post evening dose) (three assessments separated by at least 30 minutes) on Days 8, 9, and 14, and on Day 21.

[j] TETRAS (all ADL) will be performed on Day 14 and Day 21.

[k] The Empatica Wristband E4 will be worn during the Confinement Periods and on Day 14.

[l] Plasma pharmacokinetic samples will be taken predose and 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours postdose on Day 8 and predose on Days 9, 10, 11, 12, 13, and 14.

[m] Study drug will be administered in the morning with food during Part A and in the morning and evening (every 12 hours) with food during Part B.

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

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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
ADL	activities of daily living
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-t}	area under the concentration-time curve from time zero to last time point
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
BMI	body mass index
C_{max}	maximum plasma concentration
CNS	central nervous system
CRF	case report form
CS	clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DEQ-5	Drug Effects Questionnaire
ECG	electrocardiogram
eCRF	electronic CRF
ET	essential tremor
GABA	γ-aminobutyric acid
$GABA_A$	γ-aminobutyric acid-ligand gated chloride channel
$GABA_B$	γ-aminobutyric acid-G protein-coupled
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPβCD	hydroxylpropyl-β-cyclodextrin
ICF	informed consent form
ICH	International Council on Harmonisation

Abbreviation or Specialist Term	Explanation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
MTD	maximum tolerated dose
NCS	not clinically significant
NF	National Formulary
PI	Principal Investigator
PK	pharmacokinetic
QOL	quality of life
QTcF	QT interval calculated using the Fridericia method
QUEST	Quality of Life in Essential Tremor Questionnaire
SRC	Safety Review Committee
SSS	Stanford Sleepiness Scale
TEAEs	treatment-emergent adverse events
TETRAS	TRG Essential Tremor Rating Assessment Scale
$t_{1/2}$	terminal half-life
t_{max}	time to reach maximum concentration
USP	United States Pharmacopeia
VAS	visual analogue score
WHO	World Health Organization
WMA	World Medical Association

5. INTRODUCTION

5.1. Background of Essential Tremor and Unmet Medical Need

Essential tremor (ET) is among the most common neurological diseases, with an overall prevalence of 0.9%. Prevalence increases with age and is estimated to be 4.6% in people over 65 years of age (Louis 2010, Deuschl 2011). Essential tremor is largely a bilateral, symmetrical postural or kinetic tremor involving hands and forearms that is visible and persistent. Additional or isolated tremor of the head or lower limbs may occur, but in the absence of abnormal posturing (Deuschl 1998, Habib-ur-Rehman 2000). The onset of tremor has a bimodal distribution, with onset between 15 to 20 and 50 to 70 years. Over time, tremors can become more pronounced and may prevent eating, drinking, and writing, as well as executing personal hygiene like shaving or applying make-up. Voice tremors can be severe enough to inhibit talking and singing in public.

Several lines of evidence suggest that cerebellar dysfunction through the cerebellothalamocortical pathway plays a key role in ET (McAuley 2000; Pinto 2003; Elble 2009, Schnitzler 2009, Deuschl 2009). Thalamotomy and deep brain stimulation of the ventral intermediate nucleus and of the subthalamic nucleus improve ET (Deuschl 2011, Zappia 2013, Rajput 2014). Microscopic cerebellar pathology has been identified, including gliosis, Purkinje cell loss, and increased torpedoes (swellings) in the Purkinje cell axons (Louis 2007, Axelrad 2008, Shill 2008, Louis 2009). Activation studies with positron emission tomography indicate abnormally increased regional cerebral blood flow in the cerebellum both at rest and when tremor is provoked by unilateral arm extension (Boecker 1994, Wills 1996).

Essential tremor is associated with impaired γ-aminobutyric acid (GABA)ergic function (and consequent hyperactivity) in the cerebellum (Málly 1996, Bucher 1997, Louis 2007, Louis 2008, Paris-Robidas 2012). γ-aminobutyric acid, the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (γ-aminobutyric acid-ligand gated chloride channel [$GABA_A$] and γ-aminobutyric acid-G protein-coupled [$GABA_B$]) on target neurons. γ-aminobutyric acid-gated chloride channel receptors, the major class of inhibitory neurotransmitter receptors in the brain, are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents.

Drugs acting on $GABA_A$ receptors, such as primidone, benzodiazepines, or ethanol decrease tremor amplitude, suggesting that altered GABAergic neurotransmission is involved in ET. Postmortem analysis revealed a 35% reduction of $GABA_A$ receptors and a 22% to 31% reduction of $GABA_B$ receptors in the dentate nucleus of cerebella of ET subjects (Paris-Robidas 2012). Reduced levels of GABA in the cerebrospinal fluid are also reported in ET subjects (Málly 1996). Moreover, toxins such as aflatrem, penitrem A, or harmaline have been proposed to induce tremor in rodents by interacting with GABA receptors (Cavanagh 1998; Miwa 2007), and targeted deletion of the α1 subunit of $GABA_A$ receptor in knockout mice exhibits a 15 to 19 Hz action tremor, similar to ET in humans (Kralic 2005).

Consistent with the role of GABA, the majority of therapeutics for ET act by augmenting GABAergic transmission (Louis 2012, Benito-Leon 2007, Pahapill 1999). First-line treatments for ET include the anticonvulsant primidone and the β-adrenergic blocker propranolol (Gorman 1986). Like primidone, gabapentin is an anticonvulsant found to be effective in the treatment of ET (O'Brien 1981; Gironell 1999). The oldest treatment for ET is ethanol, which temporarily ameliorates tremor and is frequently used by subjects to self-medicate; however, chronic use of ethanol for tremor management carries the known risks of alcohol dependence and overuse (Pahwa 2003).

These treatments are moderately effective, reducing, though not resolving, tremor amplitudes in about 50% of the subjects (Schmouth 2014). In addition, one out of three patients abandon treatment because of side effects or poor efficacy (Louis 2010), illustrating that with few feasible treatment options and a range of handicaps in daily living makes ET an area of high unmet medical need.

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 ET. Unlike benzodiazepines that are selective for the γ-subunit-containing subset of $GABA_A$ 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 hydroxylpropyl-β-cyclodextrin [HPβCD] with 0.025 mg/mL sucralose) is a nonviscous, 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 as well as 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 which 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 are clinically complete and final clinical study reports are pending. Discussions of pharmacokinetic (PK) data are limited to the single-ascending dose, food, and essential tremor cohorts from Study 217-CLP-101 and the multiple-ascending dose and drug-drug interaction (DDI) 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 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 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.

Study 217-CLP-102 was a two-part study that assessed the effects of multiple-ascending doses of SAGE-217. 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 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 in an open-label manner to study drug-drug interactions. SAGE-217 is not likely to induce the metabolism of CYP2B6 or CYP3A4 substrates. SAGE-217 was orally bioavailable and suitable for once daily oral dosing at night time with food.

SAGE-217 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 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 (AM or PM) or 35 mg (PM) 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.

There were no clinical efficacy data of SAGE-217 in ET, since the present study is the first study in this indication.

5.4. Potential Risks and Benefits

Protocol 217-ETD-201 is the first clinical study of SAGE-217 Oral Solution in ET evaluating the efficacy of this product. 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. Many compounds that target the $GABA_A$ receptors exhibit clinical efficacy in ET, validating this receptor as a therapeutic target. Given the promising SAGE-547 clinical data 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-escalation design has been chosen to permit titration of treatment effect vs tolerability (adverse events), specifically sedation. Each subject will start with an initial dose of 10 mg to be escalated to 20 mg after a day and then escalated further to 30 mg assuming no tolerability issues. At the end of a 7-day exposure, the maximum dose for the subject will be established as will a protocol specified response. Subjects who are responders and tolerate at least the 10 mg dose for a minimum of 3 days will qualify for the randomization phase (Part B). Given the high medical need and potential for benefit in ET, there is a favorable benefit-risk evaluation to investigate SAGE-217 Oral Solution in ET.

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. STUDY OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective of this study is to compare the effect of 7 days administration of SAGE-217 Oral Solution to placebo on the change in tremor severity.

The primary endpoint of this study is the change from randomization (Day 8) in the accelerometer-based Kinesia kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) at Day 14.

6.2. Secondary Objectives

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

1. Tremor severity as assessed by the change from randomization (Day 8) in the accelerometer-based Kinesia upper limb total score (ie, the sum of forward outstretched postural tremor, lateral "wing beating" postural tremor, and kinetic tremor item scores across both sides of the body) and individual item scores at Day 14.
2. Tremor severity as measured by the change from randomization (Day 8) in TRG Essential Tremor Rating Assessment Scale (TETRAS) upper limb total score (ie, the sum of item 4c scores from both sides of the body) and individual TETRAS upper limb item scores at Day 14.
3. Tremor severity as assessed by the change from randomization (Day 8) in TETRAS Performance Subscale scores measured at Day 14.
4. Safety and tolerability as assessed by vital signs measurements, clinical laboratory data, electrocardiogram (ECG) parameters, and suicidal ideation using the Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse event reporting.
5. Sleepiness/sedation as assessed by the SSS and MOAA/S scores.
6. Mood as assessed by the Bond-Lader visual analogue score (VAS) Mood Scale.
7. How the subject feels after taking the study drug as assessed by Drug Effects Questionnaire (DEQ-5) ratings.

In addition, plasma concentrations of SAGE-217 and SAGE-217 metabolites may be measured. Pharmacokinetic parameters, such as area under the concentration-time curve from time zero to last time point (AUC_{0-t}), 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}), and terminal half-life ($t_{1/2}$), will be derived, where appropriate.

6.3. Exploratory Objectives

The exploratory objectives of the study are to compare the effect of 7 days administration of SAGE-217 Oral Solution to placebo on:

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

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

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study is a two-part, multicenter, Phase 2a study to evaluate the efficacy, safety, tolerability, and PK of SAGE-217 Oral Solution in up to 80 adult subjects with ET. Part A of the study is an open-label design with morning dosing for 7 days. Part B of the study is a double-blind, placebo-controlled, randomized withdrawal design. Subjects will be exposed to study drug (SAGE-217 or placebo) for up to 14 days and will be followed for an additional 14 days after the administration of the last dose.

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

The study will be conducted in two parts:

- Part A: Beginning on Day 1, all subjects will receive open-label SAGE-217 in the morning with food (as outlined in Section 9.2) for 7 days. Subjects will receive SAGE-217 10 mg on Day 1, SAGE-217 20 mg on Day 2, and SAGE-217 30 mg from Day 3 to Day 7, with dose adjustments for severe adverse events judged by the Investigator to be related to study drug (Section 9.3). Subjects will be confined on Day -1 through Day 3.
- Part B: In order to qualify for Part B of the study, a subject must tolerate a maximum dose of ≥10 mg of SAGE-217, and the subject must have responded to SAGE-217, defined as a 30% reduction from baseline in TETRAS kinetic tremor combined score on Day 7. Eligible subjects will be randomized in a 1:1:1 fashion to receive SAGE-217 in the morning or in the evening or to receive placebo for 7 days beginning on Day 8. All doses of study drug will be administered with food as outlined in Section 9.2. Subjects randomized to SAGE-217 will receive their maximum dose as determined in Part A. In order to preserve the blind, those randomized to SAGE-217 in the morning will receive placebo in the evening, those randomized to receive SAGE-217 in the evening will receive placebo in the morning, and those randomized to receive placebo will receive placebo in both morning and evening. Subjects randomized to the placebo arm will represent randomized withdrawal (ie, withdrawal from treatment they received in Part A). Subjects will be confined on Day 7 through Day 10.

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

7.2. Blinding and Randomization

Part A is open-label with no control group; therefore, there will be no randomization or blinding.

Part B of the study is a double-blind, placebo-controlled, randomized withdrawal study. Subjects who tolerate a maximum dose of ≥10 mg of SAGE-217 in Part A and respond to SAGE-217, defined as a 30% reduction from baseline in TETRAS kinetic tremor combined score on Day 7, will be randomly assigned in a 1:1:1 fashion to receive SAGE-217 in the morning or in the evening or placebo according to a computer-generated randomization schedule. Once it has been determined that a subject meets eligibility criteria, the subject will be sequentially assigned a subject number from the randomization schedule provided to the unblinded pharmacist. Subject identification numbers will consist of the site number (eg, "01") followed by numbering starting with double zero (eg, 01-001, 01-002, 01-003, etc.).

A randomization schedule will be generated by an independent statistical consultant for the study. This schedule will be prepared prior to the start of the study. The randomization schedule will be generated using SAS V9.2 or later. Only the clinic pharmacist, who is responsible for preparing the solutions, will be given a copy of the randomization schedule. In the event of a medical emergency, the pharmacist may reveal actual solution contents to the investigator, who should also alert Sage of the emergency (see Section 13.6 for more details related to unblinding). In all cases where the study drug allocation for a subject is unblinded, pertinent information (including the reason for unblinding) must be documented in the subject's records and on the electronic case report form (eCRF). If the subject or study center personnel (other than pharmacist) have been unblinded, the subject will be terminated from the study.

In order to preserve the blind in Part B, those randomized to SAGE-217 morning dosing will receive placebo for the evening dose, those randomized to SAGE-217 evening dosing will receive placebo for the morning dose, and those randomized to placebo will receive placebo for both morning and evening dosing. Subjects randomized to SAGE-217 will receive their maximum dose as determined in Part A. Subjects randomized to the placebo arm will represent randomized withdrawal (withdrawal from treatment they received in Part A).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

It is anticipated that up to 80 subjects will be enrolled at up to 30 study centers. The following inclusion and exclusion criteria will be applied during screening for Part A of the study.

8.1. Subject Inclusion Criteria

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

1. Subject has signed an ICF before any study-specific procedures are performed.
2. Subject must be between 18 and 75 years of age, inclusive.
3. Subject must have a diagnosis of ET, defined as bilateral postural tremor and kinetic tremor, involving hands and forearms, that is visible and persistent and the duration is >5 years prior to screening.
4. Subject must have bilateral TETRAS scores of at least two on each side (left and right) for kinetic tremor and at least two on each side (left and right) for either wing beating or forward outstretched postural tremor.
5. Subject must be willing to discontinue medications taken for the treatment of ET, alcohol, nicotine, and caffeine through Day 21 of the study.
6. Subject is in good physical health and has no clinically significant findings on physical examination, 12-lead ECG, or clinical laboratory tests.
7. Female subjects must be post-menopausal, permanently sterile (bilateral tubal occlusion), or of childbearing potential with a negative pregnancy test, non- breastfeeding, and using two highly effective methods of birth control prior to screening, throughout study participation and for 14 days after the last dose of study drug. Highly effective methods of birth control are defined as follows: hormonal (ie, established use of oral, implantable, injectable, or transdermal hormonal methods of conception); placement of an intrauterine device; placement of an intrauterine system; and mechanical/barrier method of contraception (ie, condom or occlusive cap [diaphragm or cervical/vault cap] in conjunction with spermicide [foam, gel, film, cream or suppository]).
8. 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.
9. Males must be willing to abstain from sperm donation while on study through 13 weeks after receiving the last dose of study drug.

8.2. Subject Exclusion Criteria

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

1. Subject has presence of abnormal neurological signs other than tremor or Froment's sign.
2. Subject has presence of known causes of enhanced physiological tremor.

3. Subject has or recent exposure (14 days prior to admission visit) to tremorogenic drugs, as defined in Appendix 1, or the presence of a drug withdrawal state.
4. Subject has had direct or indirect trauma to the nervous system within 3 months before the onset of tremor.
5. Subject has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.).
6. Subject has convincing evidence of sudden tremor onset or evidence of stepwise deterioration of tremor.
7. Subject has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic, or oncological disease.
8. Subject has clinically significant abnormal physical examination or 12-lead ECG at the Screening or Admission Visits. Note: A 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. An ECG may be repeated if initial values obtained exceed the limits specified.
9. Subject has a history, presence, and/or current evidence of serologic positive results for hepatitis B surface antigen (HBsAg), hepatitis C antibodies (anti-HCV), or human immunodeficiency virus (HIV) 1 or 2 antibodies.
10. Subject has hyperthyroidism.
11. Subject has used alcohol, caffeine, or nicotine within 3 days prior to Admission visit.
12. Subject has a known allergy to SAGE-217 and its major excipient HPβCD.
13. Subject has exposure to another investigational medication or device within the prior 30 days.
14. Subject has a history of suicidal behavior within 2 years or answers "YES" to questions 3, 4, or 5 on the C-SSRS at the Screening Visit or on Day -1 or is currently at risk of suicide in the opinion of the Investigator.
15. Subject has donated one or more units (1 unit = 450 mL) of blood or acute loss of an equivalent amount of blood within 60 days prior to dosing.
16. Subject is unwilling or unable to comply with study procedures.
17. Use of 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. Entrance Criteria for Part B

The following entrance criteria will be applied prior to administration of blinded study drug in Part B; subjects who require dose adjustments on Days 5, 6, and 7 of Part A will not progress to Part B.

1. Subject must tolerate a maximum dose of ≥10 mg of SAGE-217 in Part A.
2. Subject must have responded to SAGE-217, defined as a 30% reduction from baseline in TETRAS kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) on Day 7.

8.4. Subject Withdrawal Criteria

If there is an adverse event or medical reason for the withdrawal, the subject should be followed medically until the condition has either resolved itself or is stable. Details of the reason for withdrawal should be recorded in the subject's case report form (CRF).

Subjects who withdraw should, if possible, have a follow-up examination, including a physical examination, the appropriate investigations, vital signs, and clinical laboratory tests, as outlined for the Day 21 visit (Table 3). All details of this follow-up examination should be recorded in the subject's medical source documents.

8.4.1. Study Drug Withdrawal

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 failed 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 will be replaced only if they withdraw prior to dosing. Subjects who are withdrawn from the study, fail to return or are no longer qualified will not be replaced.

8.4.2. 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.

9. TREATMENT OF SUBJECTS

9.1. Number of Subjects

Approximately 80 subjects with ET will be recruited into the study to yield at least 60 randomized subjects for Part B.

9.2. Treatment Assignment

Study drug will be administered in the morning with food during Part A and in the morning and evening (every 12 hours) with food during Part B. Food intake was standardized as specified by the Sponsor.

9.2.1. Part A

Subjects participating in Part A of the study will take study drug (SAGE-217) in an open-label manner. All subjects will start on a 10 mg dose of study drug administered with food in the morning on Day 1. Subjects will receive 20 mg with food on Day 2 and 30 mg with food daily on Days 3 to 7. Dose adjustments will only be allowed 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 (Section 9.3). The dose tolerated for Days 5, 6, and 7 of the open-label dosing period will be determined to be the maximum dose for that subject.

9.2.2. Part B

Subjects participating in the double-blind, placebo-controlled, randomized withdrawal portion of the study (Part B) will be randomized to SAGE-217 morning dosing, SAGE-217 evening dosing, or placebo. Subjects randomized to SAGE-217 will receive the maximum dose of SAGE-217 from Part A of the study. Following randomization, subjects will receive 7 days of study drug starting on Day 8.

9.3. Dose Adjustment Criteria

Dose adjustments will only be allowed during the open-label phase of the study (Part A). If at any time the dose is not tolerated in Part A, assessed by occurrence of a severe adverse event judged by the investigator to be related to study drug, the dose on the next day will be reduced to the next lowest dose and continued for the remainder of the open-label dosing period (ie, subjects who are unable to tolerate the 30 mg dose will receive a lower dose of 20 mg, and subjects who are unable to tolerate 20 mg will be given a 10 mg dose). The dose tolerated for Days 5, 6, and 7 of the open-label dosing period will be determined to be the maximum dose for that subject. Subjects who require dose adjustments on Days 5, 6, and 7 of Part A will not progress to Part B.

9.4. Prior/Concomitant Medications and Restrictions

9.4.1. 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 9.4.2.

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.

9.4.2. Prohibited Medications

The drug classes listed in Appendix 1 are not permitted in the 14 days prior to the admission visit and for the duration of the study (up to the Day 21 visit). The list provides non-exhaustive examples of each drug class.

Subjects are not permitted to use alcohol, caffeine, or nicotine within 3 days prior to Admission visit through the Day 21 visit.

9.5. Treatment Compliance

Investigational product will be prepared by the site pharmacist. The Investigator(s) or designee will record the time and dose of study drug administration in the source documents. Any reasons for non-compliance will also be documented, including:

- Missed 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.

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 clinical Good Manufacturing Practice [GMP] conditions at [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.

10.2. Batch Formula for 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 by [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 (Kleptose®)	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 = hydroxylpropyl-β-cyclodextrin; NF = National Formulary; USP = United States Pharmacopeia

10.3. 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.

10.4. Study Drug Storage

Upon receipt of study drug (SAGE-217 and placebo), the Investigator or designee will inspect the medication 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 must be carefully stored at the temperature specified in the Pharmacy Manual (eg, clinical dosing solutions stored at approximately 2 to 8°C for 10 days or room temperature for up to 24 hours 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.

10.5. Administration and Study Drug Accountability

Doses will be prepared as an approximate 40 mL oral solution to be swallowed all at once, followed by approximately 200 mL of water which 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.

10.5.1. Study Drug Administration

While confined in the clinical unit (Day -1 through Day 3), subjects in Part A will receive a 10 mg dose of study drug administered in the morning on Day 1, 20 mg on Day 2, and 30 mg on Day 3.

While confined in the clinical unit in Part B (Day 7 through Day 10), subjects will receive randomized study drug in the morning and in the evening on Days 8, 9, and 10.

For non-confinement days (Days 4 through 6 [Part A] and Days 11 through 14 [Part B]), dosing will be done at the clinical site or, if suitable arrangements can be made, via home administration

where local regulations allow. Home administration of study drug will be performed according to a site-specific plan by a healthcare professional trained on the protocol and delivery of the study drug.

10.5.2. 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.

10.6. Study Drug Handling and Disposal

The pharmacist or designee for drug accountability is to document the date and time of initial compounding, subsequent admixture, administration of test article, 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 subject symptom response by a measurement of tremor amplitude, TETRAS upper limb subscale, and TETRAS Performance Subscale (items 4, 6, 7, and 8). Quality-of-life assessments include TETRAS ADL, QUEST, and video recording of subjects performing three everyday tasks. Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) will be assessed by the Empatica Wristband E4.

11.1. Measurements of Tremor Amplitude

In order to measure essential tremor amplitude, subjects will wear a wireless ring motion sensor. The motion sensor measures linear acceleration and angular velocity (the Kinesia score). Amplitudes from the motion sensor data are collected for three upper limb maneuvers (postural tremor, wing beating, kinetic tremor) on each side of the body, for a total of six amplitude measures per assessment. Data are transmitted from the sensor to a computer using Bluetooth technology. Information from the motion sensor data correlates to symptoms of tremor. The Kinesia score ranges from 0 to 4 in 0.5 step increments. Higher scores indicate more tremors. The accelerometer assessment is completed in conjunction with the TETRAS Performance Subscale Item 4.

In Part A, Kinesia will be performed predose on Day -1 (Admission; three assessments separated by at least 30 minutes) and predose and 2, 12, and 14 hours postdose (three assessments separated by at least 30 minutes) on Days 1, 2, and 7. In Part B, Kinesia will be performed before morning dose, after morning dose (2 hours post morning dose), before evening dose (12 hours post morning dose), and after evening dose (14 hours post morning dose) (three assessments separated by at least 30 minutes) on Days 8, 9, and 14, and on Day 21.

11.2. TRG Essential Tremor Rating Assessment Scale (TETRAS) Performance Scale

Item #4 (upper limb tremor) of the TETRAS Performance Subscale will be completed using both the accelerometer and clinician assessment. Testing should be completed within ±10 minutes of the planned questionnaire time points. All three tests in the upper limb tremor series of assessments (Item 4) will be completed for both arms, first for the RIGHT arm and then for the LEFT. Predose assessments can be done any time within 2 hours prior to the start of administration of solution. The Day 21 follow-up visit assessments can be done at any time during the visit.

Subjects will complete the TETRAS Performance Subscale, Item #4 (upper limb tremor) while wearing the accelerometer. Simultaneous clinician assessment of item #4 will occur. The accelerometer assessment is completed in conjunction with the TETRAS Performance Subscale at the same time points during the study.

In Part A, the TETRAS upper limb subscale will be performed at Screening, predose on Day -1 (Admission; three assessments separated by at least 30 minutes), and predose and 2, 12, and 14 hours postdose (three assessments separated by at least 30 minutes) on Days 1, 2, and 7. The

TETRAS (all ADL and Performance Subscale [Items 4, 6, 7, and 8]) will be performed on Day -1 (Admission) and on Day 7.

In Part B, the TETRAS upper limb subscale will be before morning dose, after morning dose (2 hours post morning dose), before evening dose (12 hours post morning dose), and after evening dose (14 hours post morning dose) (three assessments separated by at least 30 minutes) on Days 8, 9, and 14, and on Day 21. The TETRAS (all ADL and Performance Subscale [Items 4, 6, 7, and 8]) will be performed on Day 14 and Day 21.

Note that the bilateral TETRAS score for the test conducted during Screening will be used to determine eligibility and must be ≥2 on each side (left and right) for kinetic tremor and ≥2 on each side (left and right) for either wing beating or forward outstretched postural tremor. A copy of the TETRAS is provided in Appendix 2.

11.3. Empatica Wristband E4

Physiological activity (ie, sympathetic nervous system tone as measured by electrodermal activity, skin temperature monitoring, and heart rate monitoring) will be assessed by the Empatica Wristband E4. The Empatica Wristband E4 is a wearable motion device that captures motion-based activity and sympathetic nervous system arousal, even when the wearer is not moving. The Empatica Wristband E4 will be worn during the Confinement Periods and on Day 14. Data from the Empatica Wristband E4 will not be presented in the study report; instead, they will be part of a separate report.

11.4. Quality of Life in Essential Tremor Questionnaire (QUEST)

The QUEST is a brief, 30-item, ET-specific QOL scale in which subjects rate the extent to which tremor impacts a function or state, tremor severity in various body parts, perceived health, and overall QOL (Tröster 2005). The QUEST will be administered predose on Day -1 (Admission), Day 7, and on Day 14. A copy of the QUEST is provided in Appendix 3.

11.5. Video Recording

Videos of subjects performing three everyday tasks (drinking a glass of water, fastening a button, and one additional task that the subject experiences difficulty with on a daily basis) will be taken on Day -1 (Admission) and predose on Day 7 in Part A and on Day 14 and Day 21 in Part B.

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, 12, and 24 hours postdose on Day 1 and predose on Days 2, 3, 4, 5, 6, and 7. In Part B, plasma samples for PK analysis will be collected predose and 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hours postdose on Day 8 and predose on Days 9, 10, 11, 12, 13, and 14. 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 CRF 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 SAGE-217 will be performed utilizing a validated liquid chromatography-tandem mass spectrometry method at a qualified laboratory.

13. ASSESSMENT OF SAFETY

13.1. Safety and Tolerability Parameters

Safety and tolerability of study drug will be evaluated by vital signs measurements, clinical laboratory measures, physical examination, ECGs, concomitant medication usage, C-SSRS, SSS, MOAA/S scores, and adverse event reporting. The Bond-Lader Mood Rating Scale and a DEQ-5 will be used to assess mood and perception of drug effects, respectively.

13.1.1. Demographic/Medical History

Age, gender, race, and ethnic origin will be recorded at the Screening visit. A full medical history including medication history will be recorded at the Screening visit.

13.1.2. Vital Signs

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

In Part A, vital signs and pulse oximetry will be performed at Screening (vital signs only) and Day -1 (Admission), predose and at 1, 2, 3, 4, 6, 8, 12, 14, 16, and 24 hours postdose on Days 1, 2, and 3, predose only on Days 4, 5, 6, and 7. In Part B, vital signs and pulse oximetry will be performed predose and at 1, 2, 3, 4, 6, 8, 12, 14, 16, and 24 hours postdose on Days 8, 9, and 10, predose only on Days 11, 12, 13, and 14, and on Day 21.

13.1.3. Weight and Height

Body weight and height will be measured at the Screening visit.

13.1.4. Physical Examination

A physical examination of all major body systems will be undertaken and recorded at the Screening visit.

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, predose on Day 1, at 1, 12, and 24 hours postdose on Days 1, 2, 3, and 7. In Part B, the 12-lead ECG will be assessed at 1, 12, and 24 hours postdose on Days 8, 9, and 10, on Day 14, and on Day 21.

All time points are relative to the time of dosing.

13.1.6. Laboratory Assessments

In Part A, blood and urine samples will be collected for hematology, serum chemistry, and urinalysis at the Screening visit, on Day -1 (Admission), Day 1, and predose on Day 2. In Part B, blood and urine samples will be collected predose on Day 8, Day 9, and on Day 21.

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 13.2.1, and recorded in the eCRF.

13.1.6.1. Hematology

Hematology tests will include complete blood count, 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, AST, and 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 Test

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at the Screening visit and by urine pregnancy test on Day -1 (Admission), and at the follow-up visit on Day 28 in Part B.

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 Day -1 (Admission) (lifetime history and past 24 months). In Part A, the "Since Last Visit" C-SSRS form will be completed 12 hours postdose on Day 1, predose on Day 4, and on Days 5, 6, and 7. In Part B, the "Since Last Visit" C-SSRS form will be completed on Days 8, 11, 12, 13, and 14, on Day 21, and on Day 28. The C-SSRS is provided in Appendix 4.

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 predose and 1, 2, 3, 4, 6, 8, 12, 14, 16, and 24 hours postdose on Days 1, 2, and 3, and predose only on Days 4, 5, 6, and 7. In Part B, the SSS will be administered predose and 1, 2, 3, 4, 6, 8, 12, 14, 16, and 24 hours postdose on Days 8, 9, and 10, predose only on Days 11, 12, 13, and 14, and on Day 21. All time points are relative to the time of dosing. The SSS is provided in Appendix 5. The SSS should be performed prior to the MOAA/S score.

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 a MOAA/S score of 3 or less was observed, the score was to be confirmed by waiting approximately 10 minutes and re-administering the MOAA/S assessment. 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, 16, and 24 hours postdose on Days 1, 2, and 3, predose only on Days 4, 5, 6, and 7. In Part B, the MOAA/S will be performed predose and 1, 2, 3, 4, 6, 8, 12, 14, 16, and 24 hours postdose on Days 8, 9, and 10, predose only on Days 11, 12, 13, and 14, and on Day 21. The MOAA/S is provided in Appendix 6.

13.1.10. Bond-Lader VAS Mood Scale

Mood will be assessed using the Bond-Lader Mood Rating Scale. This is a 16-part self-administered questionnaire that employs a 100-mm VAS to explore different aspects of self-reported mood. In Part A, the mood scale will be administered predose on Days 1, 2, and 7. In Part B, the mood scale will be administered predose on Days 8, 9, and 14 and on Day 21. The Bond-Lader Mood Rating Scale is provided in Appendix 7.

13.1.11. Drug Effects Questionnaire (DEQ-5)

A DEQ-5 will be administered as follows:

1. Do you FEEL a drug effect right now?
2. Are you HIGH right now?
3. Do you DISLIKE any of the effects that you are feeling right now?

4. Do you LIKE any of the effects that you are feeling right now?
5. Would you like MORE of the drug you took, right now?

The answers are recorded on a 100-mm VAS, with the answer for each being "Not at all" and "Extremely" at the extremes. There will be options to record "Not applicable" for questions 3 and 4 if no drug effects are felt and for question 5 prior to administration of study medication. The DEQ-5 will be performed 2 hours postdose on Days 1 and 7 in Part A and 2 hours postdose on Days 8 and 14 in Part B. The DEQ-5 is provided in Appendix 8.

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 causally 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.

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, whether or not they are related to the study, must be recorded on forms provided by Sage Therapeutics or designee for the duration of the study.

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 need not record sedation as an adverse event unless 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. 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, 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.

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. 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.
Probably 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. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

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)

13.5. Reporting Serious Adverse Events

All serious adverse events (regardless of causality) will be recorded from the signing of the ICF until 14 days following the last dose of study drug. 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.

13.6. Emergency Identification of Study Drug (Part B)

Part B is a double-blind study. The pharmacist responsible for preparing the solutions will be unblinded and will retain an official paper copy of the randomization schedule.

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 eCRF. If the subject or study center personnel (other than pharmacist) have been unblinded, the subject will be terminated from the study.

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 complete at least one dose in Part B and have at least one post-randomization efficacy evaluation.

The evaluable population will consist of all randomized subjects with at least one post-randomization Kinesia assessment.

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

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, race, and ethnicity, and baseline characteristics, such as height, weight, and BMI, will be summarized.

Categorical summaries, such as race and ethnicity, 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, drug, 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. Primary Efficacy Endpoint

The change from randomization (Day 8) in the accelerometer-based Kinesia kinetic tremor combined score (ie, the sum of item 4c scores from both sides of the body) at Day 14 will be summarized by treatment group in Part B.

14.5. Secondary Efficacy Endpoints

The change from randomization (Day 8) in the accelerometer-based Kinesia upper limb total and individual item scores, TETRAS total and individual upper limb item scores, and TETRAS Performance Subscale scores at Day 14 will be summarized by treatment group in Part B.

14.6. Exploratory Efficacy Endpoints

The change from randomization (Day 8) in TETRAS ADL scores at Day 14 will be summarized by treatment group in Part B.

Empatica Wristband E4 Tremor oscillation and QUEST data will be listed by subject, study day, and time point.

A summary of clinical ratings of video recordings will be presented by group in Part B.

14.7. Safety and Tolerability Analyses

Data from vital signs, clinical laboratory measures, ECG, C-SSRS, and MOAA/S will be summarized using descriptive statistics by group and time point, where applicable. Continuous endpoints will be summarized with 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.

14.7.1. 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 7 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 and relationship to study drug (see Section 13.3).

TEAEs 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 28 follow-up visit will be listed.

14.7.2. Vital Signs

Vital sign results will be listed by subject and timing of collection. Mean changes from randomization in vital signs will be evaluated by time point.

14.7.3. Physical Examinations

Screening physical examination results will be listed by subject. Any clinically significant physical examination will be recorded in medical history.

14.7.4. 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.

14.7.5. Clinical Laboratory Evaluations

Clinical laboratory results will be listed by subject and timing of collection. Mean changes from baseline and randomization in clinical laboratory measures will be evaluated.

14.7.6. 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.

14.7.7. 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 Day 1 will be measured.

14.7.8. 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 Day 1 will be measured.

14.7.9. Bond-Lader VAS Mood Scale

Mood data collected on the Bond-Lader VAS mood scale will be listed by subject, study day, and time point. The scores and change from Day 1 will be summarized by study day and time point.

14.7.10. Drug Effects Questionnaire (DEQ-5)

Results from DEQ-5 will be listed by subject, study day, and time point. The result for each question and change from Day 1 will be summarized by study day and time point.

14.7.11. 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 part in which they are being taken. If a concomitant medication assigned to a 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.

14.8. Pharmacokinetic Analysis

Pharmacokinetic parameters will be summarized using appropriate descriptive statistics. Time to reach maximum concentration (t_{max}) will be summarized using 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.

Pharmacokinetic and pharmacodynamic modelling assessment of the relationship between plasma exposure of SAGE-217 and change from baseline in accelerometer-based Kinesia scores may be assessed.

14.9. Determination of Sample Size

Up to 80 subjects will be enrolled in Part A to yield at least 60 randomized subjects for Part B. A total sample size of 51 evaluable subjects (ie, 17 per group) will have 80% power to detect a difference in means of 3.0 on the primary endpoint assuming that the common standard deviation is 3.0 using a 2-group t-test with a 0.05 two-sided significance level. Assuming a 15% non-evaluability rate, 20 subjects per group will be randomized. The number of subjects in each treatment group is also thought to be sufficient to assess preliminary safety and tolerability following multiple doses of SAGE-217 Oral Solution.

14.10. 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 subject into the study, a representative of Sage Therapeutics or designee will visit the investigational study site to:

- Determine the adequacy of the facilities; and
- 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 CRFs, and that investigational product accountability checks are being performed;
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject'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 subject (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 CRFs 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 subject 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 CRFs.

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 CRFs 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 trial 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

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21. APPENDICES

Copies of scales and questionnaires included in Appendix 2 through Appendix 8 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. TREMOROGENIC DRUGS

The following drug classes are not permitted in the 14 days prior to the admission visit and for the duration of the study (up to the Day 21 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
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
Statins
atorvastatin

Sympathomimetics
epinephrine, pseudoephedrine
Weight loss medication
tiratricol
Xanthine derivatives
theophylline

APPENDIX 2. TRG ESSENTIAL TREMOR RATING ASSESSMENT SCALE (TETRAS)

TRG ESSENTIAL TREMOR RATING ASSESSMENT SCALE (TETRAS©) V 3.1

Activities of Daily Living Subscale

Rate tremor's impact on activities of daily living (0 - 4 scoring).

1. Speaking
0 = Normal.
1 = Slight voice tremulousness, only when "nervous".
2 = Mild voice tremor. All words easily understood.
3 = Moderate voice tremor. Some words difficult to understand.
4 = Severe voice tremor. Most words difficult to understand.

2. Feeding with a spoon
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with feeding with a spoon.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot feed with a spoon.

3. Drinking from a glass
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with drinking from a glass.
2 = Mildly abnormal. Spills a little.
3 = Moderately abnormal. Spills a lot or changes strategy to complete task such as using two hands or leaning over.
4 = Severely abnormal. Cannot drink from a glass or uses straw or sippy cup.

4. Hygiene
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with hygiene.
2 = Mildly abnormal. Some difficulty but can complete task.
3 = Moderately abnormal. Unable to do most fine tasks such as putting on lipstick or shaving unless changes strategy such as using two hands or using the less affected hand.
4 = Severely abnormal. Cannot complete hygiene activities independently.

5. Dressing
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with dressing.
2 = Mildly abnormal. Able to do everything but has difficulty due to tremor.
3 = Moderately abnormal. Unable to do most dressing unless uses strategy such as using Velcro, buttoning shirt before putting it on or avoiding shoes with laces.
4 = Severely abnormal. Cannot dress independently.

6. Pouring
0 = Normal.
1 = Slightly abnormal. Tremor is present but does not interfere with pouring.
2 = Mildly abnormal. Must be very careful to avoid spilling but may spill occasionally.
3 = Moderately abnormal. Must use two hands or uses other strategies to avoid spilling.
4 = Severely abnormal. Cannot pour.

7. Carrying food trays, plates or similar items
0 = Normal
1 = Slightly abnormal. Tremor is present but does not interfere with carrying food trays, plates or similar items.
2 = Mildly abnormal. Must be very careful to avoid spilling items on food tray.
3 = Moderately abnormal. Uses strategies such as holding tightly against body to carry.
4 = Severely abnormal. Cannot carry food trays or similar items.

8. Using Keys
0 = Normal
1 = Slightly abnormal. Tremor is present but can insert key with one hand without difficulty.
2 = Mildly abnormal. Commonly misses target but still routinely puts key in lock with one hand.
3 = Moderately abnormal. Needs to use two hands or other strategies to put key in lock.
4 = Severely abnormal. Cannot put key in lock.

9. Writing
0 = Normal
1 = Slightly abnormal. Tremor present but does not interfere with writing.
2 = Mildly abnormal. Difficulty writing due to the tremor
3 = Moderately abnormal. Cannot write without using strategies such as holding the writing hand with the other hand, holding pen differently or using large pen.
4 = Severely abnormal. Cannot write.

10. Working. If patient is retired, ask as if they were still working. If the patient is a housewife, ask the question as it relates to housework:
0 = Normal .
1 = Slightly abnormal. Tremor is present but does not affect performance at work or at home.
2 = Mildly abnormal. Tremor interferes with work; able to do everything, but with errors. .
3 = Moderately abnormal. Unable to continue working without using strategies such as changing jobs or using special equipment.
4 = Severely abnormal. Cannot perform any job or household work.

11. Overall disability with the most affected task (Name task, e.g. using computer mouse, writi etc)

Task _____

0 = Normal.
1 = Slightly abnormal. Tremor present but does not affect task.
2 = Mildly abnormal. Tremor interferes with task but is still able to perform task.
3 = Moderately abnormal. Can do task but must use strategies.
4 = Severely abnormal. Cannot do the task.

12. Social Impact

0 = None
1 = Aware of tremor, but it does not affect lifestyle or professional life.
2 = Feels embarrassed by tremor in some social situations or professional meetings.
3 = Avoids participating in some social situations or professional meetings because of tremor.
4 = Avoids participating in most social situations or professional meetings because of tremor.

Performance Subscale

Instructions

Scoring is 0 – 4. For most items, the scores are defined only by whole numbers, but 0.5 increments may be used if you believe the rating is between two whole number ratings and cannot be reconciled to a whole number. Each 0.5 increment in rating is specifically defined for the assessment of upper limb postural and kinetic tremor and the dot approximation task (items 4 and 8). All items of the examination, except standing tremor, are performed with the patient seated comfortably. For each item, score the highest amplitude seen at any point during the exam. Instruct patients not to attempt to suppress the tremor, but to let it come out.

1. Head tremor: The head is rotated fully left and right and then observed for 10s in mid position. Patient then is instructed to gaze fully to the left and then to the right with the head in mid position. The nose should be used as the landmark to assess and rate the largest amplitude excursions during the examination.

   0 = no tremor
   1 = slight tremor (< 0.5 cm)
   2 = mild tremor (0.5- < 2.5 cm)
   3 = moderate tremor (2.5-5 cm)
   4 = severe or disfiguring tremor (> 5 cm)

2. Face (including jaw) tremor: Smile, close eyes, open mouth, purse lips. The highest amplitude of the most involved facial anatomy is scored, regardless of whether it occurs during rest or activation. Repetitive blinking or eye fluttering should not be considered as part of facial tremor.

   0 = no tremor
   1 = slight; barely perceptible tremor
   2 = mild: noticeable tremor
   3 = moderate: obvious tremor, present in most voluntary facial contractions
   4 = severe: gross disfiguring tremor

3. Voice tremor: First ask subject to produce an extended "aaah" sound and eee" sound for 5 seconds each. Then assess speech during normal conversation by asking patients "How do you spend your average day?".

   0 = no tremor
   1 = slight: tremor during aaah, and eee and no tremor during speech
   2 = mild: tremor in "aaah" and "eee" and minimal tremor in speech
   3 = moderate: obvious tremor in speech that is fully intelligible
   4 = severe: some words difficult to understand

4. Upper limb tremor: Tremor is assessed during three maneuvers: forward horizontal reach posture, lateral "wing beating" posture and finger-nose-finger testing. Each upper limb is assessed and scored individually. The forward horizontal reach posture is held for 5 seconds.

The lateral wing beating posture is held for 20 seconds. The finger-nose-finger movement is executed three times. Amplitude assessment should be estimated using the maximally displaced point of the hand at the point of greatest displacement along any single plane. For example, the amplitude of a pure supination-pronation tremor, pivoting around the wrist would be assessed at either the thumb or fifth digit.

a. Forward outstretched postural tremor: Subjects should bring their arms forward, slightly lateral to midline and parallel to the ground. The wrist should also be straight and the fingers abducted so that they do not touch each other.
b. Lateral "wing beating" postural tremor: Subjects will abduct their arms parallel to the ground and flex the elbows so that the two hands do not quite touch each other and are at the level of the nose. The fingers are abducted so that they do not touch each other. The posture should be held for 20 seconds.
c. Kinetic tremor: Subjects extend only their index finger. They then touch a set object or the examiners finger located to the full extent of their reach, which is located at the same height (parallel to the ground) and slightly lateral to the midline. Subjects then touch their own nose (or chin if the tremor is severe) and repeat this back and forth three times. Only the position along the trajectory of greatest tremor amplitude is assessed. This will typically be either at the nose or at the point of full limb extension.

For all three hand tremor ratings

0 = no tremor
1 = tremor is barely visible
1.5 = tremor is visible, but less than 1 cm
2 = tremor is 1- < 3 cm amplitude
2.5 = tremor is 3- < 5 cm amplitude
3 = tremor is 5- < 10 cm amplitude
3.5 = tremor is 10- < 20 cm amplitude
4 = tremor is $\geq$ 20 cm amplitude

5. Lower limb tremor: Raise each lower limb horizontally parallel to the ground for 5 seconds each. Then perform a standard heel to shin maneuver with each leg, three times. The maximum tremor in either maneuver is scored, and only the limb with the largest tremor is scored. Tremor may exist in any part of the limb, including foot.

0 = no tremor
1 = slight: barely perceptible
2 = mild, less than 1 cm at any point
3 = moderate tremor, less than 5 cm at any point
4 = severe tremor, greater than 5 cm

6. Archimedes spirals: Demonstrate how to draw Archimedes spiral that approximately fills ¼ of an unlined page of standard (letter) paper. The lines of the spiral should be approximately 1.3 cm (0.5 inch) apart. Then ask the subject to copy the spiral. Test and score each hand separately. Use a ballpoint pen. The pen should be held such that no part of the limb touches the table. Secure the paper on the table in a location that is suitable for the patient's style of drawing. Score the tremor in the spiral, not the movement of the limb.

   0 = normal
   1 = slight: tremor barely visible.
   2 = mild: obvious tremor
   3 = moderate: portions of figure not recognizable.
   4 = severe: figure not recognizable

7. Handwriting: Have patient write the standard sentence "This is a sample of my best handwriting" using the dominant hand only. Patients must write cursively (i.e., no printing). They cannot hold or stabilize their hand with the other hand.. Use a ballpoint pen. Secure the paper on the table in a location that is suitable for the patient's style of writing. Score the tremor in the writing, not the movement of the limb.

   0 = normal
   1 = slight: untidy due to tremor that is barely visible.
   2 = mild: legible, but with considerable tremor.
   3 = moderate: some words illegible.
   4 = severe: completely illegible

8. Dot approximation task: The examiner makes a dot or X and instructs the subject to hold the tip of the pen "as close as possible to the dot (or center of an X) without touching it, (ideally approximately 1 mm) for 10 seconds ". Each hand is score separately.

   0 = no tremor
   1 = tremor is barely visible
   1.5 = tremor is visible, but less than 1 cm
   2 = tremor is 1- < 3 cm amplitude
   2.5 = tremor is 3- < 5 cm amplitude
   3 = tremor is 5- < 10 cm amplitude
   3.5 = tremor is 10- < 20 cm amplitude
   4 = tremor is $\geq$ 20 cm amplitude

9. Standing tremor: Subjects are standing, unaided if possible. The knees are 10-20 cm apart and are flexed 10-20°. The arms are down at the subject's side. Tremor is assessed at any point on the legs or trunk
   0 = no tremor
   1 = barely perceptible tremor
   2 = obvious but mild tremor, does not cause instability
   3 = moderate tremor, impairs stability of stance
   4 = severe tremor, unable to stand without assistance

Appendix 3. QUALITY OF LIFE IN ESSENTIAL TREMOR QUESTIONNAIRE (QUEST)

Quality of Life in Essential Tremor Questionnaire (QUEST)

Patient's Name: _____ ID: _____ Date: ____/____/____

Gender: ☐ Male ☐ Female Date of Birth: ____/____/____

Heath Status

In general, how would you rate your overall health? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

Overall Quality of Life

Overall, how would you rate your quality of life? (0=very poor health, 100=excellent/perfect health)

Circle: 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100

General Information

In the past month, has your tremor interfered with your sexual satisfaction?	**Y**	**N**
In the past month, have you had side effects from tremor medications?	Y	N
In the past month, have you been satisfied with the tremor control achieved by your medications?	**Y**	**N**

Which most appropriately describes your work status?

- ☐ Never worked
- ☐ Not working, retired because of tremor
- ☐ Not working, retired NOT due to tremor
- ☐ Working full time
- ☐ Working part time

TREMOR SELF ASSESSMENT

For the purposes of this questionnaire, tremor is defined as uncontrollable shaking or quivering of the body part in question.

On a typical day, how many of your waking hours do you have tremor in ANY body part?

Circle: 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Put a mark in the box to rate the severity of your tremor in each of the body parts listed below.

None - no tremor at any time
Mild - mild tremor not causing difficulty in performing any activities
Moderate - tremor causes difficulty in performing **some** activities
Marked - tremor causes difficulty in performing **most** or **all** activities
Severe - tremor **prevents** performing some activities

		None	Mild	Moderate	Marked	Severe
1.	**Head**	☐	☐	☐	☐	☐
2.	Voice	☐	☐	☐	☐	☐
3.	**Right arm/hand**	☐	☐	☐	☐	☐
4.	Left arm/hand	☐	☐	☐	☐	☐
5.	**Right leg/foot**	☐	☐	☐	☐	☐
6.	Left leg/foot	☐	☐	☐	☐	☐

continued on next page

For each question below, please mark the box which best describes your current situation.

For example: N R ~~S~~ F A

N = Never/No
R = Rarely
S = Sometimes
F = Frequently
A = Always/Yes
NA = Not Applicable

1.	My tremor interferes with my ability to communicate with others.		N R S F A
2.	My tremor interferes with my ability to maintain conversations with others.		N R S F A
3.	It is difficult for others to understand my speech because of my tremor.		N R S F A
4.	My tremor interferes with my job or profession.	NA	N R S F A
5.	I have had to change jobs because of my tremor.	NA	N R S F A
6.	I had to retire or take early retirement because of my tremor.		N A
7.	I am only working part time because of my tremor.	NA	N A
8.	I have had to use special aids or accommodations in order to continue my job due to my tremor.	NA	N R S F A
9.	My tremor has led to financial problems or concerns.		N R S F A
10.	I have lost interest in my hobbies because of my tremor.		N R S F A
11.	I have quit some of my hobbies because of my tremor.		N A
12.	I have had to change or develop new hobbies because of my tremor.		N A
13.	My tremor interferes with my ability to write (for example, writing letters, completing forms).		N R S F A
14.	My tremor interferes with my ability to use a typewriter or computer.	NA	N R S F A
15.	My tremor interferes with my ability to use the telephone (for example, dialing, holding the phone).		N R S F A
16.	My tremor interferes with my ability to fix small things around the house (for example, change light bulbs, minor plumbing, fixing household appliances, fixing broken items).		N R S F A
17.	My tremor interferes with dressing (for example, buttoning, zipping, tying shoes).		N R S F A
18.	My tremor interferes with brushing or flossing my teeth.		N R S F A
19.	My tremor interferes with eating (for example, bringing food to mouth, spilling).		N R S F A
20.	My tremor interferes with drinking liquids (for example, bringing to mouth, spilling, pouring).		N R S F A
21.	My tremor interferes with reading or holding reading material.		N R S F A
22.	My tremor interferes with my relationships with others (for example, my family, friends, coworkers).		N R S F A
23.	My tremor makes me feel negative about myself.		N R S F A
24.	I am embarrassed about my tremor.		N R S F A
25.	I am depressed because of my tremor.		N R S F A
26.	I feel isolated or lonely because of my tremor.		N R S F A
27.	I worry about the future due to my tremor.		N R S F A
28.	I am nervous or anxious.		N R S F A
29.	I use alcohol more frequently than I would like to because of my tremor.		N R S F A
30.	I have difficulty concentrating because of my tremor.		N R S F A

THANK YOU!

APPENDIX 4. COLUMBIA – SUICIDE SEVERITY RATING SCALE (C-SSRS)

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
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(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
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(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
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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 _____
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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 5. STANFORD SLEEPINESS SCALE (SSS)

Stanford Sleepiness Scale

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

Table 1. Modified Observer's Assessment of Alertness/Sedation Scale

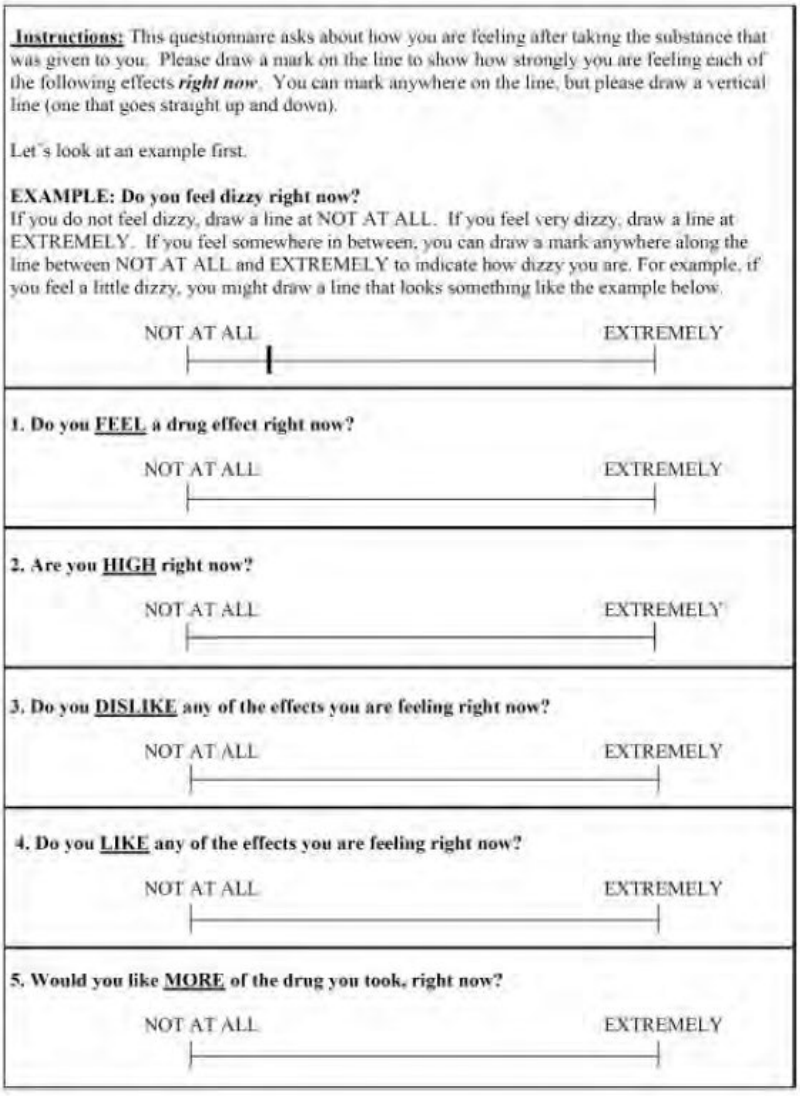
Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful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

APPENDIX 7. BOND-LADER VAS (MOOD RATING SCALE)

1. Please rate the way you feel in terms of the dimensions given below.
2. Regard the line as representing the full range of each dimension.
3. Rate your feelings as they are at the moment.
4. Mark clearly and perpendicularly across each line.

Alert	_____	Drowsy
Calm	_____	Excited
Strong	_____	Feeble
Muzzy	_____	Clear-headed
Well-coordinated	_____	Clumsy
Lethargic	_____	Energetic
Contented	_____	Discontented
Troubled	_____	Tranquil
Mentally slow	_____	Quick-witted
Tense	_____	Relaxed
Attentive	_____	Dreamy
Incompetent	_____	Proficient
Happy	_____	Sad
Antagonistic	_____	Amicable
Interested	_____	Bored
Withdrawn	_____	Gregarious

APPENDIX 8. DRUG EFFECTS QUESTIONNAIRE (DEQ-5)



Instructions: This questionnaire asks about how you are feeling after taking the substance that was given to you. Please draw a mark on the line to show how strongly you are feeling each of the following effects ***right now***. You can mark anywhere on the line, but please draw a vertical line (one that goes straight up and down).

Let's look at an example first.

EXAMPLE: Do you feel dizzy right now?
If you do not feel dizzy, draw a line at NOT AT ALL. If you feel very dizzy, draw a line at EXTREMELY. If you feel somewhere in between, you can draw a mark anywhere along the line between NOT AT ALL and EXTREMELY to indicate how dizzy you are. For example, if you feel a little dizzy, you might draw a line that looks something like the example below.

NOT AT ALL — EXTREMELY

1. Do you FEEL a drug effect right now?

NOT AT ALL — EXTREMELY

2. Are you HIGH right now?

NOT AT ALL — EXTREMELY

3. Do you DISLIKE any of the effects you are feeling right now?

NOT AT ALL — EXTREMELY

4. Do you LIKE any of the effects you are feeling right now?

NOT AT ALL — EXTREMELY

5. Would you like MORE of the drug you took, right now?

NOT AT ALL — EXTREMELY