Official Title: A Phase 2, Double-blind, Placebo-controlled, Randomized Study Evaluating The Efficacy, Safety, And Tolerability Of SAGE-324 In The Treatment Of Individuals With Essential Tremor

NCT Number: NCT04305275

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Protocol Version 3.0: 24-February-2020
Protocol Version 2.0: 20-December-2019
Protocol Version 1.0: 23-October-2019

1. PROTOCOL AND AMENDMENTS

Version Number	Date	Title
1.0	23 October 2019	A Phase 2, Double-Blind, Placebo-Controlled, Randomized Study Evaluating the Efficacy, Safety, and Tolerability of SAGE-324 in the Treatment of Individuals with Essential Tremor
2.0	20 December 2019	
3.0	24 February 2020	
4.0	10 June 2020	
5.0	17 December 2020	

Administrative Letter dated 16 November 2020

A PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED, DOSE-RANGING STUDY EVALUATING THE EFFICACY, SAFETY, AND TOLERABILITY OF SAGE-324 MONOTHERAPY AND ADJUNCTIVE THERAPY WITH PROPRANOLOL IN THE TREATMENT OF INDIVIDUALS WITH ESSENTIAL TREMOR

324-ETD-201

Investigational Product	SAGE-324 Oral Tablet
Clinical Phase	Phase 2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted], MD
Sponsor Medical Monitor	[redacted], MD, PhD
Date of Original Protocol	23 October 2019

SPONSOR APPROVAL

Protocol Number:	324-ETD-201
Study Title:	A Phase 2, Double-Blind, Placebo-Controlled, Randomized, Dose-Ranging Study Evaluating the Efficacy, Safety, and Tolerability of SAGE-324 Monotherapy and Adjunctive Therapy with Propranolol in the Treatment of Individuals with Essential Tremor
Protocol Version and Date:	Version 1.0, 23 October 2019

[redacted], MS, RAC
[redacted]
Date

[redacted], MD
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Date

[redacted], DVM
Date

[redacted]
Date

[redacted], PhD
[redacted]
Date

[redacted], PhD
[redacted]
Date

[redacted], MS
[redacted]
Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-324. I have read the 324-ETD-201 protocol 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 (DD/MMM/YYYY)

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Sage Study Physician	[redacted], MD [redacted]	Phone US: [redacted]
Sage Medical Monitor and 24-hour Emergency Contact	[redacted], MD, PhD	Office phone: [redacted] Mobile: [redacted] E-mail: [redacted]
SAE Reporting Information	IQVIA Lifecycle Safety	4820 Emperor Boulevard Durham, NC 27703 E-mail: Sage.Safety@iqvia.com Fax: 1-855-638-1674 SAE Hotline: 1-855-564-2229
Product Complaints	Sage Therapeutics, Inc.	E-mail: productcomplaints@sagerx.com Phone: 1-833-554-7243

1. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics, Inc. (hereafter referred to as Sage Therapeutics, or Sage)

Name of Investigational Product:
SAGE-324 Oral Tablet

Name of Active Ingredient:
SAGE-324

Title of Study:
A Phase 2, Double-blind, Placebo-controlled, Randomized, Dose-ranging Study Evaluating the Efficacy, Safety, and Tolerability of SAGE-324 Monotherapy and Adjunctive Therapy with Propranolol in the Treatment of Individuals with Essential Tremor

Number of Sites and Study Location: This study will take place at approximately 30 sites in the United States.

Phase of Development: Phase 2

Planned Duration for each Study Participant:
The duration of participation (from Screening through the final follow-up visit) for each participant is estimated to be up to 72 days.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the effect of SAGE-324 compared to placebo on tremor reduction in individuals with essential tremor (ET)	Change from baseline compared to placebo in Kinesia ONE™ accelerometer scores after 28 days of treatment
Secondary	
• To assess the effect of SAGE-324 compared to placebo on activities of daily living (ADLs), total performance, and upper extremities	• Change from baseline compared to placebo in Kinesia ONE accelerometer scores at all other timepoints • Change from baseline compared to placebo in the following: - The Essential Tremor Rating Assessment (TETRAS) Scale ADL score - TETRAS total performance score - TETRAS performance subscale part 4 upper limb tremor score
• To evaluate the safety and tolerability of SAGE-324	• Incidence of treatment-emergent adverse events (TEAEs)

[redacted]

Study Description:

This is a randomized, double-blind, placebo-controlled, parallel group dose-ranging study to evaluate the efficacy, safety, and tolerability of SAGE-324 as monotherapy and adjunctive therapy with propranolol in individuals with ET. Participants, site staff, and sponsor personnel will be masked to treatment allocation.

This study includes a Screening Period of up to 28 days, a 29-day treatment period (28 days of dosing), and a 14-day follow up period. After providing informed consent, participants will undergo screening assessments as outlined in Table 2 to determine eligibility.

Screening Period: The Screening Period begins with the signing of the informed consent form (ICF). Following completion of screening, on Day 1, eligible participants will visit the study center and will be randomized to 1 of 3 treatment groups (SAGE-324 30 mg daily, SAGE-324 60 mg daily, or placebo) in a 1:1:1 ratio. Randomization will be stratified based on the use of propranolol for the treatment of ET (Y/N). Participants who are on a propranolol regimen must have been on a stable dose for at least 1 month prior to Day 1 and will continue to be on a stable dose during the Treatment Period. Participants will complete baseline assessments of safety and efficacy, including the clinician-rated TETRAS and quantitative Kinesia ONE assessments of tremor, as specified in the Schedule of Assessments (Table 2).

Double-Blind Treatment Period: Starting on Day 1, participants will receive a single dose of investigational product (IP) once daily for 28 days on an outpatient basis. Doses occurring on scheduled clinic visits will be administered in the clinic, and doses occurring on all other days may be self-administered by the participant at home during the 29-day Treatment Period (28 days of dosing). During the Treatment Period, participants will return to the study center approximately once per week for efficacy and safety assessments as specified in Table 2. Participants will be trained on the use of software applications and devices necessary to complete questionnaires or other assessments as required.

Follow Up Period: Follow up visits will be conducted on an outpatient basis. Participants will continue to complete questionnaires as indicated in Table 2 and will receive a phone call approximately 7 days after the last dose of IP (ie, Day 36) for safety monitoring. Participants will return to the study center for an end of study visit approximately 14 days following the last dose of IP (ie, Day 42).

Participants who discontinue IP during the Treatment Period will be asked to return to the clinic as soon as possible for an end of treatment (EOT) visit. Follow-up visits should take place as scheduled, or relative to the last dose of IP if discontinuing treatment early. If at any time after the EOT visit, a participant decides to withdraw from the study, the participant should return for an early termination visit (ETV). The EOT and ETV can be on the same day if a participant discontinues IP and withdraws from the study on the same day during a clinic visit; in this case, all events scheduled for the EOT visit will be conducted.

During the study, a phone call will be conducted once per week (preferably mid-week) in between clinic visits, to review current status of participant.

Number of Participants (planned): Up to 120 participants, with up to 40 participants per arm.

Eligibility Criteria:

Inclusion Criteria:

1. Participant has signed an ICF before any study-specific procedures or washout of drugs is performed.
2. Participant is 18 to 80 years of age, inclusive, at the time informed consent is obtained.
3. Participant has a diagnosis of ET, as defined by all of the following criteria:
    a. Isolated tremor syndrome consisting of bilateral upper limb action tremor
    b. At least 3 years duration
    c. With or without tremor in other locations (eg, head, voice, or lower limbs)
    d. Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism, isolated focal tremors (eg, voice, head), task- and position-specific tremors, sudden tremor onset or evidence of step-wise deterioration of tremor
4. Participant has a combined total upper extremity TETRAS score of ≥8 with at least 1 upper extremity TETRAS score >4.
5. Participant is willing to discontinue medications taken for the treatment of ET, with the exception of propranolol, within 14 days or 5 half-lives (whichever is longer) prior to receiving IP.
6. Participants taking propranolol for the treatment of ET must be on a stable dose for at least 1 month prior to Day 1 and must be willing to maintain their stable dose through Day 29.
7. Participant is willing to discontinue the use of alcohol and drugs of abuse within at least ≥1 week prior to Day 1 and through Day 29 of the study.
8. Female participant agrees to use at least one method of highly effective contraception as listed in Section 8.2.4 during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does include abstinence).
9. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 13 weeks after receiving study drug, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 8.2.4.
10. Male participant is willing to abstain from sperm donation for the duration of the study and for 13 weeks after receiving study drug.
11. Female participant must have a pregnancy test result that is confirmed as negative at Screening and Day 1.
12. At the discretion of the Investigator, participant is medically stable and ambulatory, and has been on stable dose(s) of any necessary prescription or over the counter medication(s) for at least 30 days prior to Day 1, or changes/discontinues their use prior to Day 1 with the appropriate washout, as applicable per investigator judgement.

13. Participant has no clinically significant findings, as determined by the investigator, on physical examination including mental state examination (MSE) and neurologic examination, 12-lead ECG, or clinical laboratory tests.

Exclusion Criteria:

1. Participant has presence of known causes of enhanced physiological tremor.
2. Participant has had recent exposure (14 days prior to Day 1) to tremorgenic drugs or presence of a drug or alcohol withdrawal state.
3. Participant has had direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor.
4. Participant has had a previous procedure for the treatment of ET, deep brain stimulation, brain lesioning, or magnetic resonance (MR) guided procedure, eg, MR-guided focused ultrasound.
5. Participant has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.)
6. Participant has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic (hypothyroidism with stable thyroid replacement is acceptable), or oncological disease.
7. Participant has 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.
8. Participant has history of alcohol or drug abuse within 6 months prior to Screening, or a positive screen for alcohol on the Day 1 visit, or a positive screen for drugs of abuse at Screening or at the Day 1 visit.
9. Participant has a known allergy to SAGE-324 or any excipient.
10. Participant has had exposure to another investigational drug or device within 30 days prior to the Day 1 visit.
11. Participant has history or suicidal behavior within 2 years or answers “YES” to questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk or suicide in the opinion of the investigator
12. Participant has donated one or more units (1 unit = 450 mL) of blood or experienced acute loss of an equivalent amount of blood within 60 days prior to Day 1.
13. Participant is unable to perform Kinesia ONE assessments or unable to use the device required to perform the assessment.
14. Participant has any condition or comorbidity that in the opinion of the investigator would limit or interfere with the participant’s ability to complete or partake in the study.
15. Participant is unwilling or unable to comply with study procedures and required training.
16. Participant has used any known moderate or strong cytochrome P450 3A4 or P450 2D6 inhibitors and/or inducers within 14 days or 5 half-lives (whichever is longer) prior to Day 1 or consumed grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St.

John's Wort or products containing these within 30 days prior to Day 1. Use of mild cytochrome inhibitors and/or inducers may be permitted.

17. Participant has concurrent or recent exposure (14 days prior to the Day 1 visit) to sedative/hypnotic drugs, stimulants, eg, opioids, highly-caffeinated beverages or dietary supplements containing high doses of caffeine, or recent increase above regular daily consumption of coffee.
18. Participant has concurrent or recent exposure (30 days prior to the Day 1 visit) to long-acting benzodiazepines.
19. Participant plans to undergo elective surgery or relocate during participation in the study.
20. Participant is investigative site personnel or a member of their immediate families (spouse, parent, child or sibling whether biological or legally adopted).

Investigational Product Dosage and Mode of Administration:

Study drug, SAGE-324 or matched placebo oral tablet(s) will be administered in the clinic or self-administered once daily, in the morning with food. The following dose levels of SAGE-324 will be evaluated:

- 30 mg daily in the morning
- 60 mg daily in the morning

Duration of Treatment:

Each participant will receive a single dose of SAGE-324 oral tablet or matching placebo administered once daily for 28 days.

Statistical Methods:

A separate statistical analysis plan (SAP) will provide a detailed description of the data analyses to be performed in the study. The SAP will be finalized and approved prior to database lock.

General Considerations

For the purpose of all efficacy and safety analyses where applicable, baseline is defined as the last measurement prior to the start of IP administration.

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

Analysis Sets

The Randomized Set is defined as all participants who are randomized.

The Safety Set will include all participants who were administered IP.

The Full Analysis Set will include all randomized participants who received any amount of IP and have a baseline and at least one postbaseline clinic-based Kinesia ONE accelerometer score.

[redacted]

The Per Protocol Set will include all participants in the Full Analysis Set without any major protocol deviations that could affect efficacy. The review of major protocol deviations will be completed, and the decision on whether the deviation affects efficacy will be documented before database unblinding.

Determination of Sample Size

The sample size of this study is based on the assumption of a 3 points difference in the mean change from baseline Kinesia ONE accelerometer scores between SAGE-324 and placebo with a standard deviation of 3.5 points and a 1:1:1 randomization schedule. Under these assumptions, a sample size of 30 evaluable subjects per group would provide 90% power assuming a 2-sided test at α level of 0.05. By including 3 treatment groups and using a 1:1:1 randomization ratio, a total of 90 evaluable subjects are required. Assuming a nonevaluability rate of 25%, at least 120 subjects will be randomized.

Analysis of Primary Efficacy Endpoint

The estimand for the primary efficacy analysis is the treatment difference between either dose of SAGE-324 and placebo in mean change from baseline in clinic-based Kinesia ONE accelerometer scores at Day 29 based on Full Analysis Set. This will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline Kinesia ONE accelerometer score, stratification factor, assessment timepoint, and timepoint-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline clinic visits will be included in the model. The main comparison will be between SAGE-324 and placebo at the 29-day timepoint. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz compound symmetry or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not unstructured, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

Analysis of Secondary Efficacy Endpoints

Similar to those methods described above for the primary endpoint, an MMRM will be used to analyze of the change from baseline in TETRAS total performance scores, TETRAS Performance subscale part 4 upper limb tremor scores and TETRAS ADL scores.

Safety Analysis

Safety and tolerability of study drug will be evaluated by incidence of TEAEs/serious adverse events,

[redacted]

Table 2: Schedule of Assessments

Assessment	Screening	Treatment Period									Follow-up Period			
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15 (±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**32 (±1) Phone Call**	**35 Safety Phone Call**	**38 (±1) Phone Call**	**42 (±1) EOS/ ETV[a]**
Informed Consent	X													
Inclusion/Exclusion	X													
Demographics	X													
Medical History	X													
Hepatitis/HIV screen	X													
Pregnancy Test (all women)	X (serum; all women)	X (urine; WOCBP only)				X (urine; WOCBP only)				X (urine; WOCBP only)				X (urine; WOCBP only)
FSH (postmenopausal women only)	X													
Randomization[b]		X												
Drug/alcohol screens	X	X		X		X		X		X				X
Physical examination[c]	X	X		X		X		X		X				X
Neurological examination including MSE[c]	X	X		X		X		X		X				X
Body height	X									X				X
Body weight	X	X		X		X		X		X				X
Vital signs[d]	X	X		X		X		X		X				X
12-Lead ECG[e]	X	X		X		X		X		X				X
Chemistry/hematology/ coagulation/urinalysis	X	X		X		X		X		X				X
[redacted]														

Assessment	Screening	Treatment Period									Follow-up Period			
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15 (±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**32 (±1) Phone Call**	**35 Safety Phone Call**	**38 (±1) Phone Call**	**42 (±1) EOS/ ETV[a]**
[redacted]														
Kinesia[g]	X	X		X		X		X		X				X
Investigational Product Diary training[h]	X													
TETRAS[i]	X	X		X		X		X		X				X
[redacted]														
Patient Perception of Response Burden										X				X
Participant training[j]	X													

Assessment	Screening	Treatment Period									Follow-up Period			
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15 (±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**32 (±1) Phone Call**	**35 Safety Phone Call**	**38 (±1) Phone Call**	**42 (±1) EOS/ ETV[a]**
Dispense study drug		X		X		X		X						
IP administration		Administered once daily for 28 days								Not applicable				
AEs/SAEs	X													
Prior and concomitant medication and history[k]	X													

Abbreviations: ADL = activities of daily living; AE = adverse event; [redacted]; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; [redacted]; ETV = early termination visit; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; ICF = informed consent form; min = minutes; IP = investigational product; MSE = mental state examination; [redacted]; SAE = serious adverse event; TETRAS = The Essential Tremor Rating Assessment Scale; WOCBP = women of childbearing potential

Note:

- A phone call will be performed once, mid-week between clinic visits during the Treatment Period, and once per week during the Follow-Up Period. During the phone call, the current status of the participant will be reviewed, including but not limited to, AE reporting and characterization, IP compliance review, and assessment of general well-being. Days 1, 8, 15, 22, and 29 are clinic visits.
- The suggested order of assessments during clinic visits is: vital signs, Kinesia, TETRAS, ECG, blood sample collection for [redacted] clinical laboratory assessments, and questionnaires.
- All Day 1 assessments will be performed predose.

[a] Participants who discontinue IP during the treatment period should return to the site for an EOT visit as soon as possible. Participants who discontinue IP will be encouraged to continue on study and complete safety assessments and follow-up visits. Follow-up visits should take place as scheduled relative to the last dose of IP. If at any time after the EOT visit, a participant decides to withdraw from the study, the participant should return for an ETV. The EOT and ETVs can be on the same day if a participant discontinues IP and withdraws from the study on the same day during a clinic visit. In such case, all procedures scheduled for EOT and ETV will be conducted.

[b] Randomization will occur on Day 1 only. In addition to meeting all other eligibility criteria, eligibility is determined based on the total upper extremity TETRAS score of ≥8 with at least 1 upper extremity TETRAS score >4 at Screening.

[c] Complete physical examinations (including MSE and neurologic examination as parts of physical examination) should be performed as specified and as clinically necessary (see Section 11.1.3).

[d] Vital signs without orthostatic blood pressure and heart rate will be collected predose in the beginning of each visit and again prior to departing the clinic, at approximately 5 hours (±30 min). Postdose vital signs to include orthostatic blood pressure and heart rate, measured after the participant has been in the supine position for at least 5 minutes and then repeated 1 minute and 3 minutes after standing.

[e] ECGs will be collected and read centrally. ECGs will be performed approximately 5 hours (±30 min) postdose. All ECGs must be performed after the participant has been in a supine position for at least 5 minutes.

[redacted]

[g] Kinesia ONE will be assessed simultaneous to TETRAS Performance subscale part 4 upper limb tremor. On clinic dosing days, participants will perform Kinesia ONE assessments approximately 30 to 60 minutes prior to dosing in the morning. In addition, on Day 15, Kinesia ONE assessments will be performed at 5 and 8 hours (±30 min) postdose.

[h] Training specific to the Investigational Product Diary will be performed prior to randomization.

[i] The TETRAS Performance and TETRAS ADL subscales will be assessed at Screening and predose at each clinic visit postrandomization. The TETRAS Performance subscale part 4 upper limb tremor will be assessed simultaneous to Kinesia ONE. In addition, on Day 15, the TETRAS Performance subscale will be assessed at 5 and 8 hours (±30 min) postdose. Eligibility is determined based on the combined TETRAS performance subscale part 4 upper limb tremor total score ≥8, with at least 1 upper limb score >4 at Screening.

[j] Participants will be trained on the use of software applications and devices necessary for the conduct of the study by site personnel.

[k] Prior and concomitant medications will be recorded during Screening and will include all medications and supplements taken within the 30 days prior to signing the ICF through the first dose of IP. Concomitant medications will be recorded thereafter throughout the duration of the study. At Screening, this will include year of diagnosis and history of treatments for ET since year of diagnosis and use of antidepressant medications taken in the prior 12 months.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ADL	activities of daily living
AUC_{inf}	area under the curve from 0 to infinity
$AUC_{0\text{-}tau}$	area under the concentration-time curve from 0 to end of the dosing period
BMI	body mass index
[redacted]	[redacted]
C_{max}	maximum observed concentration
CRO	contract research organization
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End-of-Study
[redacted]	[redacted]
[redacted]	[redacted]
ET	essential tremor
[redacted]	[redacted]
ETV	early termination visit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
[redacted]	[redacted]
PI	principal investigator
PK	pharmacokinetic
[redacted]	[redacted]

Abbreviation	Definition
[redacted]	[redacted]
PV	pharmacovigilance
QTcF	QT corrected according to Fridericia's formula
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
t_{max}	time of occurrence of C_{max}
WHO	World Health Organization

4. INTRODUCTION

SAGE-324 is a positive allosteric modulator (PAM) of A-type γ-aminobutyric acid-gated chloride channel ($GABA_A$) receptors, the major class of inhibitory neurotransmitter receptors in the brain. In addition to being developed as an adjunctive therapy in epilepsy and other seizure disorders under IND 139201, SAGE-324 is also being developed for the treatment of Essential Tremor (ET).

Essential tremor is a permanently debilitating, neurologically determined, common movement disorder characterized by involuntary rhythmic oscillation of a body part due to intermittent muscle contractions typically occurring when not at rest, thus interfering with fine motor skills associated with daily activities (Olanow 2008, Deuschl 2011, Hopfner 2016, NIH 2019). Although the pathophysiology and etiology of ET is not fully understood, it is postulated that approximately 50% of ET patients feature an autosomal dominant pattern of familial inheritance and that non-inherited cases may have toxin-based or other causality (Olanow 2008, Hopfner 2016). ET is the most common movement disorder in the US, with prevalence estimated to be approximately 2.2% of the population, representing a substantial societal medical burden with over an estimated 7 million ET patients in the US alone (Louis 2014).

In general, active tasks of daily life are adversely impacted by ET, including but not limited to speech, handwriting, household tasks, and occupational demands, contributing negatively to psychosocial well-being, general anxiety, and overall quality of life (Koller, 1989). Although benign in term of its effect on life expectancy, ET is a progressive neurodegenerative condition whose symptoms are typically disabling, often forcing patients to change jobs or seek early retirement (Zappia, 2013). In some cases, serious disability may ensue.

The pharmacological profile of SAGE-324 is theorized to induce therapeutic effect in the treatment of ET. Based on preclinical studies of SAGE-324, which features a different mechanism of action than that of propranolol, the pharmacokinetic (PK)/ pharmacodynamic (PD) profile suggests SAGE-324 may safely ameliorate symptoms in patients suffering from ET, regardless of propranolol use.

There are currently ongoing Phase 1 clinical studies of SAGE-324 in healthy adults and in adults with ET. These studies, in addition to preclinical studies of SAGE-324, are detailed in the investigator's brochure.

With a $GABA_A$ receptor-based mechanism of action featuring positive allosteric modulation capability, SAGE-324 represents a novel approach to treatment of ET with possible utility as monotherapy or adjunctive to propranolol, which may help address the unmet medical need of the ET population, warranting further study of SAGE-324 as a potential treatment for this common movement disorder.

Henceforth, this double-blind, placebo-controlled efficacy and safety study of SAGE-324 will be conducted in adults with and without concomitant use of propranolol and is designed to assess the effect of SAGE-324 on a variety of outcome measures specific to ET disease characteristics and associated quality of life domains.

4.1. Dose Justification

Doses of SAGE-324 planned for this study are 30 mg and 60 mg given as oral tablets, to be administered once daily in the morning with food. The doses were selected based on preliminary data from 3 active studies of SAGE-324, which included: unblinded data from completed cohorts in 324-CLP-101 Part A (oral solution SAGE-324 doses of 3 mg, 10 mg, 30 mg, 45 mg, 60 mg); Part C (oral solution SAGE-324 doses of 30 mg); Part D (oral suspension SAGE-324 doses of 30 mg) in healthy subjects; and preliminary data from open-label Part E (oral suspension SAGE-324 doses of 45 mg and 60 mg) in participants with ET; additional preliminary data from 324-CLP-102 cohorts 1 through 6 (cohorts 1 to 5 unblinded, cohort 6 blinded), which evaluated oral suspension doses ranging from 5 mg to 60 mg; and preliminary unblinded data from 324-CLP-104, which compared the relative bioavailability of the oral tablet (30 mg) vs oral suspension (30 mg) formulations of SAGE-324 and separately the effect of food on the PK of the SAGE-324 oral tablet. In 324-CLP-101 and 324-CLP-102 studies, doses were administered in a fasted state. The preliminary data from all of these active studies collectively informed the route of administration (oral) and dose strengths of 30 mg and 60 mg as oral tablets planned for further evaluation in this study.

SAGE-324 was generally well-tolerated in participants with ET and in healthy volunteers, as was shown in the preliminary data of 324-CLP-101 Part E at single administration doses of 45 mg and 60 mg, and in 324-CLP-102 through once-daily administered doses of up to 60 mg for 14 days. In addition, tremor reduction was observed at both doses on TETRAS and Kinesia accelerometry, with greater improvement seen at 60 mg compared to 45 mg.

In the clinically complete study 324-CLP-104, preliminary data showed that SAGE-324 oral tablets, when coadministered with a meal, resulted in exposures approximately equivalent to that of SAGE-324 oral suspension under fasted conditions. Therefore, the SAGE-324 oral tablets are recommended to be administered with food.

4.2. Benefit/Risk Assessment

Based on the mechanism of action of SAGE-324 and the results of completed nonclinical studies and preliminary data of currently ongoing clinical studies of SAGE-324, it is theorized that participants may have symptomatic amelioration, ie, tremor reduction and possibly improved quality of life from potentially stabilizing disease characteristics associated with ET.

Potential risks anticipated in this study are based on available data from toxicology studies of SAGE-324 in addition to preliminary data from 3 ongoing, currently active Phase 1 clinical studies of SAGE-324.

As of 18 October 2019, based on the preliminary clinical data available, there have been no deaths, SAEs related to IP, or confirmed clinically significant trends in clinical laboratory evaluations, vital signs, or physical examinations. Available preliminary clinical data is summarized in the Investigator's Brochure.

Based on available preliminary clinical data from SAGE-324 active clinical studies, AEs of somnolence and feeling of relaxation are considered adverse drug reactions. In addition to scheduled clinic visits, the current status of study participants will be reviewed via weekly phone calls, in between clinic visits.

5. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the effect of SAGE-324 compared to placebo on tremor reduction in individuals with essential tremor (ET)	• Change from baseline compared to placebo in Kinesia ONE™ accelerometer scores after 28 days of treatment
Secondary	
• To assess the effect of SAGE-324 compared to placebo on activities of daily living (ADLs), total performance, and upper extremities	• Change from baseline compared to placebo in Kinesia ONE accelerometer scores at all other timepoints • Change from baseline compared to placebo in the following: - The Essential Tremor Rating Assessment (TETRAS) Scale ADL score - TETRAS Total Performance Score - TETRAS Performance Subscale Part 4 Upper Limb Tremor
• To evaluate the safety and tolerability of SAGE-324	• Incidence of treatment-emergent adverse events (TEAEs)
[redacted]	

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled, parallel group dose-ranging study to evaluate the efficacy, safety, and tolerability of SAGE-324 as monotherapy and adjunctive therapy with propranolol in individuals with ET. Participants, site staff, and sponsor personnel will be masked to treatment allocation (see Section 8.5).

This study includes a Screening Period of up to 28 days, a 29-day treatment period consisting of 28 days of dosing with the end of treatment visit intended to be on Day 29 at trough, and a 14-day follow-up period relative to final dose (Figure 1). After providing informed consent, participants will undergo screening assessments as outlined in Table 2 to determine eligibility.

The Screening Period begins with the signing of the informed consent form (ICF). Following completion of screening, on Day 1, eligible participants will visit the study center and will be randomized to 1 of 3 treatment groups (SAGE-324 30 mg, SAGE-324 60 mg, or placebo) in a 1:1:1 ratio. Randomization will be stratified based on the use of propranolol for the treatment of ET (Y/N). Participants who are on a propranolol regimen must have been on a stable regimen for at least 1 month prior to Day 1 and will continue to be on that stable regimen during the Treatment Period. Participants will complete baseline assessments of safety and efficacy, including the clinician-rated TETRAS and quantitative Kinesia ONE assessments of tremor, as specified in the Schedule of Assessments (Table 2).

During the double-blind Treatment Period, starting on Day 1, participants will receive a single dose of investigational product (IP) once daily for 28 days on an outpatient basis. Doses occurring on scheduled clinic visits will be administered in the clinic, and doses occurring on all other days will be self-administered by the participant at home as specified in Table 2. During the Treatment Period, participants will return to the study center approximately once per week for efficacy and safety assessments as specified in Table 2. In addition, a phone call will be conducted once per week (preferably mid-week) in between clinic visits, to review current status of the participant.

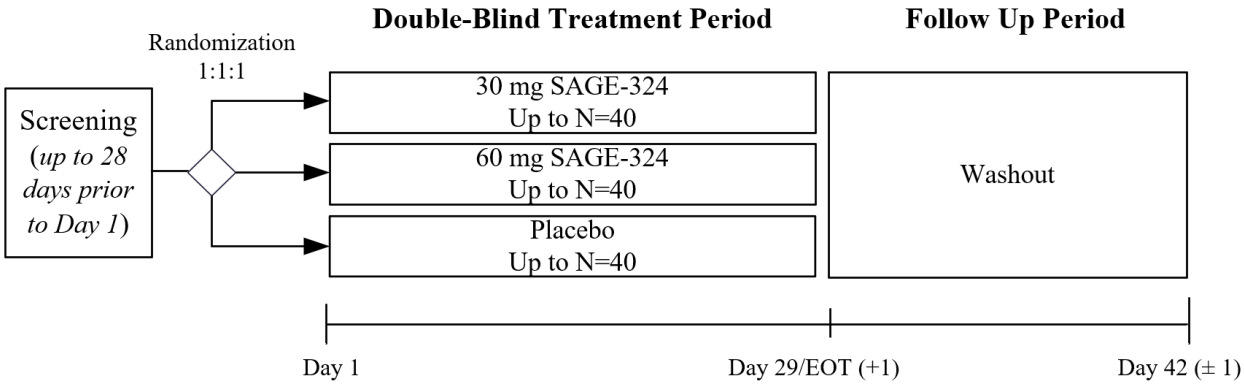
In addition to Kinesia ONE-specific training, clinical study center staff and study participants will be trained on the use of software applications and devices necessary to complete questionnaires or other assessments as required. During in-clinic visits, clinical study center staff will be available to assist participants as needed, to ensure they can access and use the software applications and devices correctly according to the training.

During the follow-up period, visits will be conducted on an outpatient basis. In addition to the phone calls to review current status, participants will receive a phone call approximately 7 days after the last dose of IP (ie, Day 35) for safety monitoring. Participants will return to the study center for an end of study visit approximately 14 days following the last dose of IP (ie, Day 42).

Participants who discontinue IP during the Treatment Period will be asked to return to the clinic as soon as possible for an end of treatment (EOT) visit. Follow-up visits should take place as scheduled, or relative to the last dose of IP if discontinuing treatment early. If at any time after the EOT visit, a participant decides to withdraw from the study, the participant should return for an early termination visit (ETV). The EOT and ETV can be on the same day if a participant

discontinues IP and withdraws from the study on the same day during a clinic visit; in this case, all events scheduled for the EOT visit will be conducted.

Figure 1: Study Design



Abbreviation: EOT = end of treatment

6.2. Number of Participants

Up to approximately 120 participants are planned, with up to 40 participants enrolled per arm, to produce an estimated 30 participants per arm who will complete the study. Additional participants may be randomized if the drop-out rate is higher than anticipated (ie, >25%).

6.3. Treatment Assignment

Participants will be assigned to 30 mg or 60 mg IP (active or placebo) in accordance with the randomization schedule on Day 1. Additional details on randomization and blinding are provided in Section 8.5.

6.4. Dose Adjustment Criteria

Doses will not be adjusted for this study except as clinically necessary, eg, interrupting dose due to an AE or serious adverse event (SAE) considered related to IP, or as recommended by the medical monitor in consultation with the investigator.

6.5. Criteria for Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to participants, 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 IRB/ethics committee (EC), where required, and initiate withdrawal procedures for participating participants.

7. SELECTION AND WITHDRAWAL OF PARTICIPANTS

7.1. Participant Inclusion Criteria

Participants must meet all of the following criteria to qualify for participation in this study:

1. Participant has signed an ICF before any study-specific procedures or washout of drugs is performed.
2. Participant is 18 to 80 years of age, inclusive, at the time informed consent is obtained.
3. Participant has a diagnosis of ET, as defined by all of the following criteria:
    a. Isolated tremor syndrome consisting of bilateral upper limb action tremor
    b. At least 3 years duration
    c. With or without tremor in other locations (eg, head, voice, or lower limbs)
    d. Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism, isolated focal tremors (eg, voice, head), task- and position-specific tremors, sudden tremor onset or evidence of step-wise deterioration of tremor
4. Participant has a combined total upper extremity TETRAS score of ≥8 with at least 1 upper extremity TETRAS score >4.
5. Participant is willing to discontinue medications taken for the treatment of ET, with the exception of propranolol, within 14 days or 5 half-lives (whichever is longer) prior to receiving IP.
6. Participants taking propranolol for the treatment of ET must be on a stable dose for at least 1 month prior to Day 1 and must be willing to maintain their stable dose through Day 29.
7. Participant is willing to discontinue the use of alcohol and drugs of abuse within at least ≥1 week prior to Day 1 and through Day 29 of the study.
8. Female participant agrees to use at least one method of highly effective contraception as listed in Section 8.2.4 during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does include abstinence).
9. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 13 weeks after receiving study drug, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 8.2.4.
10. Male participant is willing to abstain from sperm donation for the duration of the study and for 13 weeks after receiving study drug.
11. Female participant must have a pregnancy test result that is confirmed as negative at Screening and Day 1.

12. At the discretion of the investigator, participant is medically stable and ambulatory, and is on stable dose(s) of any necessary prescription or over-the-counter medication(s) for at least 30 Days prior to Day 1, or changes/discontinues their use prior to Day 1 with the appropriate washout, as applicable per investigator judgement.
13. Participant has no clinically significant findings, as determined by the investigator, on physical examination including mental state examination (MSE) and neurologic examination, 12-lead ECG, or clinical laboratory tests.

7.2. Participant Exclusion Criteria

Participants who meet any of the following criteria are disqualified from participation in this study:

1. Participant has presence of known causes of enhanced physiological tremor.
2. Participant has had recent exposure (14 days prior to Day 1) to tremorgenic drugs or presence of a drug or alcohol withdrawal state.
3. Participant has had direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor.
4. Participant has had a previous procedure for the treatment of ET, deep brain stimulation, brain lesioning, or magnetic resonance (MR) guided procedure, eg, MR-guided focused ultrasound.
5. Participant has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.)
6. Participant has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic (hypothyroidism with stable thyroid replacement is acceptable), or oncological disease.
7. Participant has 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.
8. Participant has history of alcohol or drug abuse within 6 months prior to Screening, or a positive screen for alcohol on the Day 1 visit, or a positive screen for drugs of abuse at Screening or at the Day 1 visit.
9. Participant has a known allergy to SAGE-324 or any excipient.
10. Participant has had exposure to another investigational drug or device within 30 days prior to the Day 1 visit.
11. Participant has history or suicidal behavior within 2 years or answers “YES” to questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk or suicide in the opinion of the investigator
12. Participant has donated one or more units (1 unit = 450 mL) of blood or experienced acute loss of an equivalent amount of blood within 60 days prior to Day 1.

13. Participant is unable to perform Kinesia ONE assessments or unable to use the device required to perform the assessment.
14. Participant has any condition or comorbidity that in the opinion of the investigator would limit or interfere with the participant's ability to complete or partake in the study.
15. Participant is unwilling or unable to comply with study procedures and required training.
16. Participant has used any known moderate or strong cytochrome P450 3A4 or P450 2D6 inhibitors and/or inducers within 14 days or 5 half-lives (whichever is longer) prior to Day 1 or consumed grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St. John's Wort or products containing these within 30 days prior to Day 1. Use of mild cytochrome inhibitors and/or inducers may be permitted.
17. Participant has concurrent or recent exposure (14 days prior to the Day 1 visit) to sedative/hypnotic drugs, stimulants, eg, opioids, highly-caffeinated beverages or dietary supplements containing high doses of caffeine, or recent increase above regular daily consumption of coffee.
18. Participant has concurrent or recent exposure (30 days prior to the Day 1 visit) to long-acting benzodiazepines
19. Participant plans to undergo elective surgery or relocate during participation in the study.
20. Participant is investigative site personnel or a member of their immediate families (spouse, parent, child or sibling whether biological or legally adopted).

7.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned IP or entered in the study, ie, a participant who does not meet 1 or more of the eligibility criteria after providing consent and prior to randomization (Day 1). A minimal set of screen failure information will be collected, including demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

7.4. Investigational Product Discontinuation and Early Termination from the Study

7.4.1. Investigational Product Discontinuation

A participant may withdraw from the study at any time at his/her own request for any reason. The investigator may discontinue a participant from the study and/or from IP for safety, behavioral, compliance, or administrative reasons. Participants who elect to discontinue IP will be encouraged by the Investigator to remain on study and complete the 14-day follow-up safety assessments.

The reason for IP discontinuation and/or the reason for early termination from the study must be documented in the participant's study record and recorded in the participant's electronic case report form (eCRF).

The investigator must notify the sponsor and/or the medical monitor when a participant stops participation in the study for any reason.

If a participant is persistently noncompliant, the investigator should discuss with the sponsor the potential discontinuation of the participant. Any reasons for unwillingness or inability to adhere to the protocol must be recorded in the participant's eCRF, including:

- missed visits;
- interruptions in the schedule of study drug administration;
- nonpermitted medications

Participants who discontinue IP due to an AE, regardless of investigator-determined causality, should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant.

7.4.2. Early Termination from the Study

At the time of study withdrawal/stopping study participation, if possible within 48 hours of final IP dose, an ETV/EOT visit should be conducted as specified in the Schedule of Assessments (Table 2). The participant will be permanently discontinued both from the IP and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor will retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.4.3. Loss to Follow-up

A participant will be deemed lost to follow-up after 3 attempts at contacting the participant have been unsuccessful.

7.4.4. Replacement of Participants

Participants will not be replaced.

8. TREATMENT OF PARTICIPANTS

8.1. Description of Investigational Product

SAGE-324 is an orally administered tablet provided in 5 mg tablets totaling 30-mg and 60-mg doses, to be administered once daily for 28 days, proceeded by a 14-day follow-up period. IP doses are to be administered in the morning with food.

Participants in all cohorts will receive the appropriate dose of IP (30 mg total dose of SAGE-324 tablets, 60 mg total dose of SAGE-324 tablets, or appearance-matched placebo tablets) according to the randomization schedule. Additional details regarding IP preparation, formulation, and storage are included in Section 9.

8.2. Prior Medications, Concomitant Medications, Restrictions, and Contraception Requirements

8.2.1. Prior and Concomitant Medications and/or Supplements

The start and end dates, route, dose/units, frequency, and indication for all medications and/or supplements taken within 30 days prior to signing the informed consent through the first dose of IP will be recorded. Use of antidepressant medications taken in the prior 12 months will be recorded at Screening; all other medications taken within the 30 days prior to Screening will be recorded.

All medications and/or supplements taken from the first dose of IP through the Day 42 (±1 days) visit (including start and end dates route, dose/units, frequency, and indication) will be recorded on the eCRF. Any concomitant medication determined necessary for the welfare of the participant may be given at the discretion of the investigator at any time during the study.

8.2.2. Prohibited Medications

Use or consumption of the following is prohibited for the timeframes specified:

- Treatment with an investigational drug or device during the 30 days or 5 half-lives (if known) of the investigational drug, whichever is longer, prior to Screening or during the study
- Use of any prescription or over-the-counter medication (except for propranolol use as prescribed, and/or up to 3 g/day of acetaminophen), herbal medication, vitamins, or mineral supplements within 14 days prior to first IP administration, or during the study period
- Use of tremorgenic drugs or agents known to affect SAGE-324 drug metabolism (any known CYP450 3A4 inhibitors and/or inducers) within the 28 days or 5 terminal half-lives (whichever is longer) prior to first IP administration or during the study period

8.2.3. Other Restrictions

In addition to alcohol and drugs of abuse, the following are not permitted during the study, or within 14 days of the first IP dose: sedative/hypnotic drugs, stimulants, eg, opioids, benzodiazepines, highly-caffeinated beverages or dietary supplements containing caffeine.

8.2.4. Acceptable Forms of Contraception

Acceptable forms of highly effective contraception for participants of childbearing potential or for partners of male participants who are of childbearing potential include:

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal ligation or bilateral tubal occlusion (performed at least 3 months prior to Screening)
- Vasectomized partner (performed at least 3 months prior to Screening)
- Sexual abstinence (no sexual intercourse)

Acceptable forms of contraception for male participants include:

- Sexual abstinence (no sexual intercourse)
- History of vasectomy (performed at least 3 months prior to Screening)
- Condom with spermicide used together with highly effective female contraceptive methods if the female partner(s) is of childbearing potential (see above for list of acceptable female contraceptive methods)

8.3. Intervention after the End of the Study

There is no planned intervention following the end of the study.

8.4. Treatment Adherence

The first dose of IP will be received and administered by participants in the clinic. Participants will be dispensed a 7-day supply of IP to orally self-administer at home with instructions specifying to administer in the morning with food. Treatment adherence will be monitored by the site staff at each in-clinic visit by direct questioning and counting returned tablets and will be documented. Details on drug accountability are included in Section 9.6.

8.5. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Participants will be randomized in a stratified manner based on propranolol for the treatment of ET (Y/N); randomization will be done within each stratum in a 1:1:1 ratio to treatment groups (SAGE-324 30 mg, SAGE-324 60 mg, or placebo). Participants, site staff, and the sponsor will be blinded to treatment allocation. Randomization schedules will be generated by an independent statistician. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

8.5.1. Emergency Unblinding

During the study, the blind is to be broken only when the safety of a participant is at risk and the treatment plan is dependent on the study treatment received. Unless a participant is at immediate risk, the Investigator should make diligent attempts to contact Sage prior to unblinding the study treatment administered to a participant. Requests from the investigator about the treatment administered to study participants should be discussed with the Sage Medical Monitor. If the unblinding occurs without Sage's knowledge, the investigator must notify Sage within 24 hours of breaking the blind. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

In all cases where the IP allocation for a participant is unblinded, pertinent information (including the reason for unblinding) must be documented in the participant's records and on the eCRF. At the time of withdrawal from the study/stopping participation, if possible, an EOT and/or ETV should be conducted.

If a participant or study personnel become unblinded to treatment, the participant will be excluded from the Per Protocol analysis set, as detailed further in the statistical analysis plan.

9. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

9.1. Investigational Product

Table 3: Investigational Product

	Investigational Product	
Product Name:	SAGE-324	Placebo
Dosage Form:	Tablet	Tablet
Tablet Strength	5 mg	0 mg
Route of Administration	Oral	Oral
Physical Description	Immediate release white to off-white, round, film-coated tablet containing 5 mg of SAGE-324 drug substance, and composed of lactose, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and fumed silica, featuring Opadry® II white as the coating agent.	Immediate release white to off-white, round, film-coated tablet containing no drug substance, composed of lactose, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and fumed silica, featuring Opadry® II white as the coating agent.
Manufacturer	Sage Therapeutics, Inc.	

9.2. Investigational Product Packaging and Labeling

SAGE-324 Oral Tablets and Placebo Tablets will be packaged in blinded, high density polyethylene (HDPE) containers. The containers used for SAGE-324 and placebo will be identical in appearance. The package labeling conforms to FDA and GMP requirements.

9.3. Investigational Product Storage

Upon receipt of the IP, the investigator, or the responsible pharmacist or designee, will inspect the product and acknowledge receipt in accordance with the study-specific process.

The IP must be carefully stored at the temperature specified in the investigator's brochure, securely and separately from other drugs. The IP may not be used for any purpose other than the present study. After the study is completed, all unused IP must be returned per the sponsor's instructions or destroyed locally per the site's procedure(s). IP may not be destroyed until accountability and reconciliation procedures have been completed and monitored.

The Investigator or designee will be responsible for ensuring appropriate storage, dispensing, inventory, and accountability of the IP. An accurate, timely record of the disposition of the IP must be maintained.

9.4. Investigational Product Preparation

The IP will be in tablet form and provided in blinded packaging. No preparation is required for the tablet, which is administered orally as described below.

9.5. Investigational Product Administration

The first dose of IP will be administered in the clinic, and at home thereafter as specified in the Schedule of Assessments (Table 2). The IP will be provided as tablets in dosage according to the randomized dose cohort (30 mg or 60 mg) and will be orally administered once daily in the morning, with food.

9.6. Investigational Product Accountability, Handling, and Disposal

Upon receipt of IP, the investigator(s), or the responsible pharmacist or designee, will inspect the IP and complete and follow the instructions regarding receipt and storage in the investigator's brochure and (where applicable) in the Pharmacy Manual. A copy of the shipping documentation will be kept in the study files.

The designated site staff will dispense the supplied participant-specific kits to participants at the planned dispensation visit intervals outlined in the Schedule of Assessments (Table 2).

Site staff will access the interactive response technology (IRT) at the Screening Visit to obtain a participant identification (ID) number for each participant who has signed an ICF. On Day 1, site staff will access the IRT and provide the necessary participant-identifying information, including the participant ID number assigned at Screening, to randomize the eligible participant into the study and obtain the medication ID number for the IP to be dispensed to that participant. The medication ID number must be recorded.

At the subsequent IP-dispensing visit, the investigator or designee will access the IRT, providing the same participant ID number assigned at Screening, to obtain the medication ID number for the IP to be dispensed at that visit. The medication ID number, and the number of tablets returned by the participant at this visit must be recorded.

If dispensing errors or discrepancies are discovered by site staff or sponsor's designee, the sponsor must be notified immediately.

The IP provided is for use only as directed in this protocol. The investigator or designee must keep a record of all IP received, used and returned/discarded.

Sage Therapeutics will be permitted access to the study supplies at any time with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

The investigator, pharmacist, or qualified designee is responsible for drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

At the end of the study, any unused IP tablets will be returned to Sage Therapeutics for destruction or destroyed locally per the site's procedures; disposition of IP will be documented.

9.7. Product Complaints

A product complaint is any written, electronic, or verbal expression of dissatisfaction regarding the identity, quality, reliability, safety, purity, potency, effectiveness or performance (applicable for approved marketed products) of a drug product after it is released for distribution.

In the course of conduct of the study, study personnel may become aware of a product complaint associated with the use of a Sage product. Personnel shall notify Sage within 24 hours by forwarding the product complaint information via the contact information listed in Table 1 and in the Pharmacy Manual. Where possible, personnel should segregate and retain any product, materials, or packaging associated with the product complaint until further instruction is provided by Sage or its designated representative(s).

10. EFFICACY ASSESSMENTS AND CLINICAL PHARMACOLOGY ASSESSMENTS

10.1. Efficacy Assessments

10.1.1. Kinesia ONE™ Accelerometer Score

Kinesia ONE™ is an ISO-certified wireless motion sensor worn distally on the index finger, which utilizes 3 orthogonal accelerometers and 3 orthogonal gyroscopes to monitor three-dimensional motion. Data is transmitted wirelessly from the sensor to a Bluetooth technology-enabled device to use with the Kinesia ONE software (eg, Apple iPad or similar device with preinstalled Kinesia ONE software). The device has received FDA clearance.

Via the Kinesia ONE software application, measures of three-dimensional motion are converted to scores ranging from 0 to 4, per assessed maneuver; higher scores indicate greater tremor severity. Motion in both arms is captured.

Participants will complete this assessment at each clinic visit as specified in the Schedule of Assessments (Table 2).

10.1.2. The Essential Tremor Rating Assessment Scale

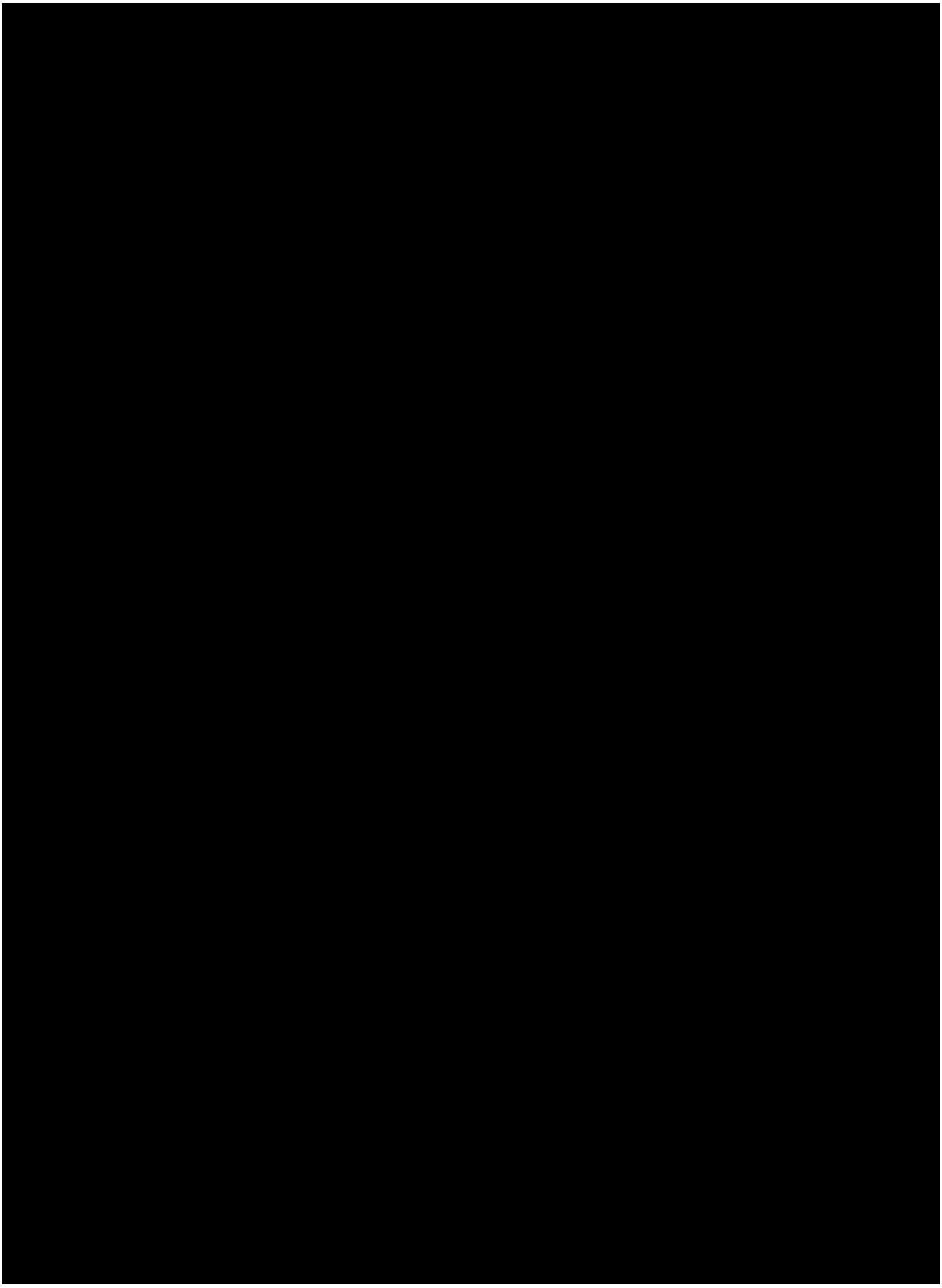
TETRAS is a validated, comprehensive clinical assessment of essential tremor (Elble 2013).

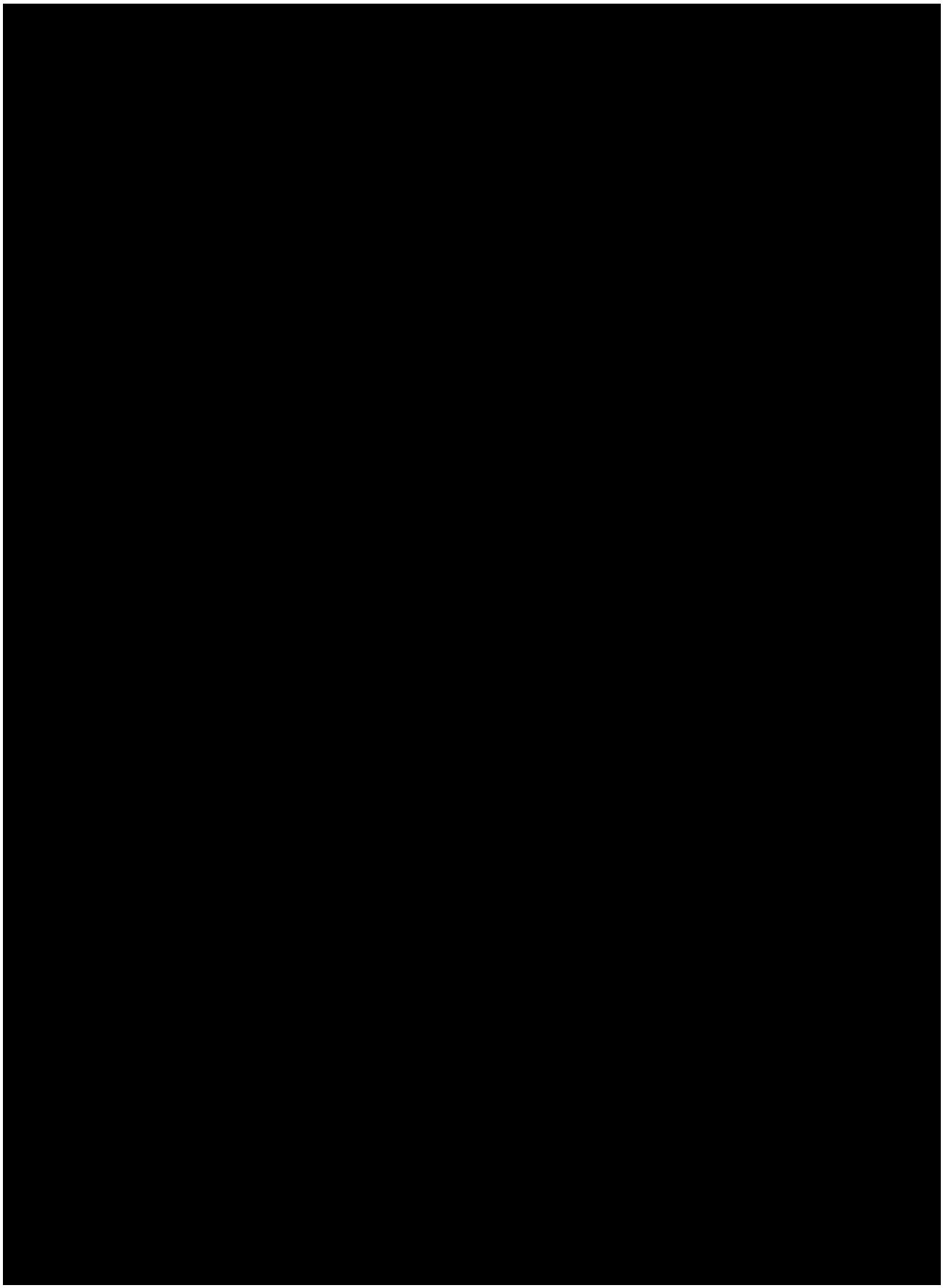
Three different components of TETRAS will be assessed in this study. The TETRAS ADL subscale, total performance score, and performance subscale part 4 upper limb tremor score, and will each be separately assessed at each clinic visit as specified in the Schedule of Assessments (Table 2).

The ADL subscale assesses how ET is impacting typical activities of daily living (ie, speech, eating, drinking, dressing, personal hygiene, writing, occupational impairment, social impact, and activities affected by upper limb tremor). It consists of 12 items that are each rated in from 0 (normal activity) to 4 (severe abnormality). The overall ADL score range is 0 to 48.

The total performance score is based on overall rating of the performance subscale, which measures tremor amplitude in the voice, limbs, head, face, trunk, and also measures functional task capabilities, ie, handwriting, spirography, and holding a pen over a dot. Each of these items is rated on a scale from 0 (no tremor) to 4 (severe tremor). Collectively, the performance items generate an overall performance score from 0 to 64.

For the performance subscale part 4 upper limb tremor score, all 3 maneuvers in the upper limb assessments of part 4 (subscale items 4a, 4b, and 4c) will be completed for both arms, first for the left arm and then for the right. The part 4 subscale ordinally rates postural (limbs extended forward maneuver, and wing-beating [elbows flexed] maneuver), and kinetic (finger-nose-finger maneuver) tremor on a 0 to 4 severity scale in 0.5-point increments.





[redacted]

10.3. Other Patient-Reported Assessments

10.3.1. Patient Perception of Response Burden

The Patient Perception of Response Burden Questionnaire is a patient-reported measure that assesses the multidimensional construct of response burden (Atkinson 2019).

Participants respond to 6 items assessing 1) how well the questions related to their actual concerns, 2) how comfortable the participants were with answering the questions, 3) how well the survey characterized their health and well-being, 4) the length of time to complete the questionnaires, 5) whether questions seemed unimportant or repetitive, and 6) what additional information should have been gathered. Items 1 to 3 are assessed on a 0 to 10 scale, item 4 is assessed on a 1 to 3 scale, and items 5 and 6 are open-ended. Items 1 and 4 are reverse scored. A composite score can be calculated to create a weighted representative index of relevance, comfort, and well-being relative to time to completion (ie, items 1, 2, and 3 were summed and multiplied by item 4) for a range of 0 to 72, with higher scores indicative of elevated endorsed response burden. The open-ended items will be summarized thematically. The Patient Perception of Response Burden Questionnaire will be performed as specified in the Schedule of Assessments (Table 2).

11. SAFETY ASSESSMENTS

11.1. Safety Parameters

All assessments will be conducted according to the Schedule of Assessments (Table 2).

11.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, ethnicity) and a full medical history will be documented. This must also additionally include participant recall of history of ET, disease duration, past treatments used, and responsiveness to alcohol and/or other treatments with use intended as off-label treatment of ET (eg, primidone or similar therapies).

11.1.2. Weight and Height

Height and weight will be measured and documented. Body mass index (BMI) will be calculated and documented.

11.1.3. Physical Examination

Whenever possible, the same individual should perform all physical examinations. Physical examinations will include assessment of body systems (eg, head, eye, ear, nose and throat; heart; lungs; abdomen; and extremities) as well as cognitive and neurological examination and MSE. Unscheduled physical examinations may also be conducted per the Investigator's discretion.

Any abnormality in physical examinations will be interpreted by an investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents.

11.1.4. Vital Signs

Vital signs comprise heart rate, respiratory rate, temperature, and blood pressure. Systolic and diastolic blood pressure are to be measured after the participant has been supine for at least 5 minutes prior to the measurement. When assessed postdose, orthostatic blood pressure and heart rate will also be measured after the participant has been in the supine position for at least 5 minutes and then repeated approximately 1 and 3 minutes after standing.

Any abnormality in vital signs will be interpreted by an Investigator as abnormal, NCS; or abnormal, CS in source documents.

11.1.5. Electrocardiogram

A 12-lead ECG will be performed. The standard intervals (heart rate, PR, QRS, QT, and QTcF) as well as any rhythm abnormalities will be recorded.

Electrocardiograms will be performed after the participant has been resting in a supine position for at least 5 minutes. When ECG measurements coincide with safety assessments, vital signs assessment or blood draws, procedures should be carried out in said order (vital signs, ECG, blood draw).

All abnormal ECGs will be interpreted by an investigator as abnormal, NCS, or abnormal, CS in source documents.

11.1.6. Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected. Analytes to be evaluated are summarized in Table 4.

Table 4: Summary of Clinical Laboratory Analytes

Biochemistry	*Renal Panel*: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate *Hepatic Panel*: albumin, ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, total protein, lactate dehydrogenase, gamma glutamyl transferase *Other*: triglycerides, cholesterol (low density lipoprotein [LDL], high density lipoprotein [HDL]), creatine phosphokinase, thyroid stimulating hormone (TSH)
Coagulation	activated partial thromboplastin time, prothrombin time, and international normalized ratio
Hematology	red blood cell count, hemoglobin, hematocrit, white blood cell count with differential, platelet count, and if red blood count indices are abnormal, reflex red blood cell morphology as indicated
Urinalysis	protein, glucose, pH, blood, leukocytes, leukocyte estrase, urobilinogen, bilirubin, ketones, nitrite
Virus Serology (Screening only)	hepatitis B antigen; hepatitis C antibodies; HIV-1 and -2 antibodies

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, NCS; or abnormal, CS in source documents.

Follicle stimulating hormone testing will be conducted to confirm whether a participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal (Section 7.1).

11.1.6.1. Drugs of Abuse, Alcohol, Cotinine

Separate urine samples for assessment of selected drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, THC, stimulants, and opiates), cotinine, and alcohol will be collected.

11.1.6.2. Pregnancy Screen

A serum pregnancy test will be conducted for all female participants at Screening; a urine pregnancy test will be conducted for all participants of childbearing potential as specified in the Schedule of Assessments (Table 2).

[redacted]

11.1.8. Safety Phone Call

A phone call will be conducted once per week, preferably mid-week in between clinic visits (as specified in Table 2), to collect information about current health status, general well-being, IP compliance, or to gather other pertinent health-related information as per investigator judgement.

11.2. Adverse Events and Serious Adverse Events

11.2.1. Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

A TEAE is defined as an AE with onset after the start of IP, or any worsening of a preexisting medical condition/AE with onset after the start of IP and throughout the study. The term IP includes any Sage IP, a comparator, or a placebo administered in a clinical trial.

Laboratory abnormalities [redacted] are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be clinically significant. Any abnormalities that meet the criteria for an SAE should be reported in an expedited manner. Laboratory abnormalities [redacted] that are clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

All AEs that occur after any participant has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be reported to Sage Therapeutics.

Participants who discontinue the IP due to an AE, regardless of investigator-determined causality, should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant. Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The sponsor or its representative retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

11.2.2. Serious Adverse Event (SAE) Definition

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Places the participant at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

An SAE may also be any other medically important event that, in the opinion of the Investigator may jeopardize the participant or may require medical intervention to prevent 1 of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

All SAEs that occur after any participant has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE report form provided by Sage Therapeutics. Any SAE that is ongoing when the participant completes their final study visit, will be followed by the investigator until the event has resolved, stabilized, returned to baseline status, or until the participant dies or is lost to follow up.

A prescheduled or elective procedure or routinely scheduled treatment will not be considered an SAE, even if the participant is hospitalized. The site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or on a waiting list to be scheduled) prior to obtaining the participant's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress, in the opinion of an Investigator, between the participant's consent to participate in the study and at the time of the procedure or treatment.

11.2.3. Definition of Adverse Events of Special Interest

There are no known adverse events of special interest as of the date of signature approval of this clinical protocol.

11.2.4. Relationship to Investigational Product

The investigator must make the determination of relationship to the IP for each AE (not related, related). The following definitions should be considered when evaluating the relationship of AEs and SAEs to the IP.

Not Related	An AE will be considered "not related" to the use of the IP if there is not a reasonable possibility that the event has been caused by the IP. Factors pointing towards this assessment include but are not limited to: the lack of temporal relationship between administration of the IP and the event, the presence of biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE
Related	An AE will be considered "related" to the use of the IP if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point towards this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of alternative explanation for the AE

11.2.5. Recording Adverse Events

AEs spontaneously reported by the participant 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. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, outcome and seriousness (if applicable), and whether or not it caused the participant to discontinue the IP or withdraw early from the study.

Intensity will be assessed according to the following scale:

- Mild: symptom(s) barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s)
- Moderate: symptom(s) of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptom(s) may be needed
- Severe: symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with IP; treatment for symptom(s) may be given and/or participant hospitalized

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 11.2.2. An AE of severe intensity may not necessarily be considered serious.

11.2.6. Reporting Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE(s), the study site must notify Sage or designee within 24 hours of the study site staff becoming aware of the SAE(s). The investigator must complete, sign and date the SAE report form, verify the accuracy of the information recorded on the SAE report form with the corresponding source documents, and send a copy to Sage or designee.

Additional follow-up information, if required or available, should all be sent to Sage or designee within 24 hours of receipt on a follow-up SAE report form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

SAEs occurring after the designated follow up time for the study, should be reported to Sage or designee according to the timelines noted above only if the Investigator considers the SAE related to IP.

Sage, or designee, is responsible for notifying the relevant regulatory authorities of certain events. It is the principal investigator's responsibility to notify the IRB/EC of all SAEs that occur at his or her site. Investigators will also be notified of all suspected unexpected serious adverse reactions (SUSARs) that occur during the clinical study. Each site is responsible for notifying its IRB of all SUSARs.

In addition, appropriate personnel in Sage Drug Safety and Pharmacovigilance or designee will unblind SUSARs for the purpose of regulatory reporting. Sage or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Sage, or designee, will submit SUSARs to investigators in a blinded fashion.

11.3. Pregnancy

If a participant becomes pregnant after the first administration of IP, pregnancy information must be collected and recorded on the pregnancy form and submitted to the sponsor within 24 hours of learning of the pregnancy. Details will be collected for all pregnancies for which conception was likely to have occurred after the start of IP administration until 5 terminal half-lives following the last administration of IP or until the completion of the study whichever is longer. Any pregnancy occurring in that time frame will be followed until delivery or termination of the pregnancy. The investigator will also attempt to collect pregnancy information on any participant's partner who becomes pregnant after the participant has received the first administration of IP. After obtaining the necessary signed informed consent from the pregnant partner directly, the investigator will follow the same pregnancy reporting procedures specified for pregnant participants.

The participant or participant's partner will be followed to determine the outcome of the pregnancy. The outcome of all pregnancies (eg, spontaneous abortion, elective abortion, normal birth) must be followed and documented even if the participant was discontinued from the study. The investigator will collect follow-up information on the participant or participant's partner and the neonate, and the information will be forwarded to Sage or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication. Any complication during pregnancy (eg, anemia, infections, preeclampsia) should be reported as an AE/SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death,), the investigator should follow the procedures for reporting an SAE.

11.4. Overdose

An overdose is any dose of study treatment given to a participant or taken by a participant that exceeds more than one extra tablet within 24 hours as described in protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded.

12. STATISTICS

Detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock. Any changes or additions to the SAP following database lock will be described in detail in the clinical study report.

12.1. Data Analysis Sets

The Randomized Set will include all participants who are randomized.

The Safety Set will include all participants administered IP.

The Full Analysis Set will include all randomized participants who received any amount of IP and have a baseline and at least one postbaseline Kinesia ONE accelerometer score.

[redacted]

The Per Protocol Set will include all participants in the Full Analysis Set without any major protocol deviations that could affect efficacy. The review of major protocol deviations will be completed, and the decision on whether the deviation affects efficacy will be documented before database unblinding.

12.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All participants will be used in the analyses, as per the analysis populations, using all nonmissing data available. No imputation process will be used to estimate missing data.

12.3. General Considerations

All participant data, including those that are derived, that support the tables and figures will be presented in the participant data listings. Some data may be presented only in participant data listing, some may be presented with a corresponding table or figure; these will be indicated in relevant sections below. Participants will be summarized according to treatment received.

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to receipt of IP.

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

12.4. Demographics and Baseline Characteristics

Demographic data, such as age, race, and ethnicity, and baseline characteristics, such as height, weight, and BMI, will be summarized using the Safety Set.

Pregnancy test results and drug screen results will be listed but not summarized.

Medical history will be listed by participant.

12.5. Efficacy Analysis

The estimand for the primary efficacy analysis is the treatment difference between either dose of SAGE-324 and placebo in mean change from baseline in clinic-based Kinesia ONE accelerometer scores at Day 29 based on the Full Analysis Set. This will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline Kinesia ONE accelerometer score, stratification factor, assessment timepoint, and timepoint-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline clinic visits will be included in the model. The main comparison will be between SAGE-324 and placebo at the 29-day timepoint. Model-based point estimates (ie, least squares means, 5% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz compound symmetry or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not UN, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

Similar to those methods described above for the primary endpoint, an MMRM will be used for the analysis of the change from baseline in TETRAS total performance scores, TETRAS performance subscale part 4 upper limb tremor scores and TETRAS ADL scores.

Other efficacy analyses will be specified in the SAP. In general, data will be analyzed using appropriate descriptive statistics or prespecified statistical methods as applicable; participant listings will be provided for all efficacy data. Participants will be analyzed according to randomized treatment for the purpose of efficacy unless otherwise specified.

Sensitivity analyses will be described in the SAP.

12.6. Safety Analyses

Safety and tolerability of SAGE-324 will be evaluated by AEs, concomitant medication usage, [redacted] Safety data will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Set using treatment received.

12.6.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or higher. A treatment-emergent adverse event (TEAE) is defined as an AE with onset after the first dose of IP. The analysis of AEs will be based on the concept of TEAEs. The incidence of TEAEs will be summarized by System Organ Class (SOC) and preferred term. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to IP.

Any TEAEs leading to discontinuation of treatment or withdrawal from the study and any treatment-emergent SAEs will be summarized.

All AEs and SAEs (including those with onset or worsening before the start of IP) through the end of the study will be listed.

[redacted]

12.6.3. Physical Examinations

The occurrence of a physical examination, including MSE, (yes/no) and the date performed will be listed by participant.

[redacted]

12.6.6. 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 (WHO-DD) September 2015, or later.

All medications taken within 30 days prior to informed consent through the duration of the study will be recorded. In addition, all psychotropic medications taken in the previous 30 days prior to screening will be recorded. Those medications taken prior to the initiation of the start of IP will be denoted “Prior”. Those medications taken prior to the initiation of the IP and continuing beyond the initiation of the IP or those medications started at the same time or after the initiation of the IP will be denoted “Concomitant”.

Medications will be presented according to whether they are “Prior” or “Concomitant” as defined above. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Details of prior and concomitant medications will be listed by participant, start date, and verbatim term.

[redacted]

12.8. Sample Size and Power

The sample size of this study is based on the assumption of a 3 points difference in the change from baseline Kinesia ONE accelerometer between SAGE-324 and placebo with a standard deviation of 3.5 points and a 1:1:1 randomization schedule. Under these assumptions, a sample size of 30 evaluable participants per group would provide 90% power for detecting a placebo-adjusted treatment difference of 3 points in Kinesia accelerometer assuming a 2-sided test at αlevel of 0.05. By including 3 treatment groups and using a 1:1:1 randomization ratio, a total of 90 evaluable participants are required. Assuming a nonevaluability rate of 25%, at least 120 subjects will be randomized.

12.8.1. Interim and Data Monitoring Committee (DMC) Analyses

Not applicable.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Sage Therapeutics will visit the investigational study site per Sage SOPs to:

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

During the study, a monitor from Sage Therapeutics or representative 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 case report forms, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the participant'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 participant (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or EC.

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

13.2. Audits and Inspections

Sage Therapeutics or authorized representatives of Sage Therapeutics, a regulatory authority, or an independent EC or an IRB may visit the site to perform an audit(s) or inspection(s), including source data verification. The purpose of a Sage Therapeutics audit or a regulatory authority 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/ICH GCP guidelines, and any applicable regulatory requirements. The Investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency or IRB/EC about an inspection.

13.3. Institutional Review Board or Ethics Committee

The principal investigator must obtain IRB (or EC) approval for the clinical study prior to enrolling a participant. Initial IRB (or EC) approval, and all materials approved by the IRB (or EC) for this study including the participant consent form and recruitment materials must be maintained by the investigator and made available for inspection.

14. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practice and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit(s) at the clinical site. Please see Section 13.2 for more details regarding the audit process.

The Investigator must have adequate quality control practices to ensure that the study is performed in a manner consistent with the protocol, GCP/ICH GCP guidelines, and applicable regulatory requirements. The investigator is responsible for reviewing all identified protocol deviations. Significant protocol deviations should be reported to the IRB/EC per the IRB/EC's written procedures.

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. When the investigator retains the services of any individual or party to perform trial-related duties and functions, the Investigator must ensure the individual or party is qualified to perform trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed, and any data generated.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained, if necessary to provide clarification.

15. ETHICS

15.1. Ethics Review

The final study protocol, including the final version of the ICF, must be given a written and dated approval or favorable opinion by an IRB or EC as appropriate. The Investigator must obtain and document approval before he or she can enroll any participant into the study. The IRB or EC must supply to the sponsor a list of the IRB/EC membership and a statement to confirm that the IRB/EC is organized and operates according to GCP and applicable laws and regulations.

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

The principal investigator is also responsible for providing the IRB or EC with reports of any reportable serious adverse drug reactions from any other study conducted with the IP. Sage Therapeutics will provide this information to the principal investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or EC according to local regulations and guidelines. In addition, the principal investigator must inform the IRB/EC and sponsor of any changes significantly affecting the conduct of the trial and/or increasing the risk to participants (eg, violations to the protocol or urgent safety measures taken for participant safety).

15.2. 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 are consistent with ICH and GCP guidelines, as well as all applicable regional or national regulatory requirements.

15.3. Written Informed Consent

Prior to enrolling a trial participant, the investigator(s) will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and allowed time to consider the information provided.

When the participant decides to participate in the trial, the participant (or the participant's, parent or legally authorized representative) must provide signed and dated informed consent. The written consent must be obtained before conducting any study procedures. The investigator must document the consent process in the participant's source records. The investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant or to the participant's parent or legally authorized representative.

Throughout the trial participants should be informed of any changes made to the study and as new safety and or risk information becomes known. The provision of this information will be documented in the participant's source records, and when applicable, an updated ICF will be provided.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

Sage Therapeutics or its representative(s) will be allowed to conduct site visits at the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the facility, drug storage area, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

Inspection of the study by a regulatory authority may occur at any time. The investigator must agree to the inspection of study-related records and source documents by the regulatory authority representative(s).

16.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for the period outlined in the site contract, or for a period of 2 years after the last marketing application approval, and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Sage is responsible to inform the Investigator/institution as to when study documents no longer need to be retained.

17. PUBLICATION POLICY

All information concerning SAGE-324 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.

18. LIST OF REFERENCES

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A PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY EVALUATING THE EFFICACY, SAFETY, AND TOLERABILITY OF SAGE-324 MONOTHERAPY AND ADJUNCTIVE THERAPY WITH PROPRANOLOL IN THE TREATMENT OF INDIVIDUALS WITH ESSENTIAL TREMOR

324-ETD-201

Investigational Product	SAGE-324 Oral Tablet
Clinical Phase	Phase 2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted], MD
Sponsor Medical Monitor	[redacted], MD, PhD
Date of Original Protocol	23 October 2019
Date of Amendment 1	20 December 2019

SPONSOR APPROVAL

Protocol Number:	324-ETD-201
Study Title:	A Phase 2, Double-Blind, Placebo-Controlled, Randomized Study Evaluating the Efficacy, Safety, and Tolerability of SAGE-324 Monotherapy and Adjunctive Therapy with Propranolol in the Treatment of Individuals with Essential Tremor
Protocol Version and Date:	Version 2, 20 December 2019

[redacted]

[redacted], MS, RAC

Date

[redacted]

[redacted], MD

Date

[redacted]

[redacted], DVM

Date

[redacted]

[redacted], PhD

Date

[redacted]

[redacted], PhD

Date

[redacted]

[redacted], MS

Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-324. I have read the 324-ETD-201 protocol 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 (DD/MMM/YYYY)

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Sage Study Physician	[redacted], MD	Phone [redacted]
Sage Medical Monitor and 24-hour Emergency Contact	[redacted], MD, PhD	Mobile: [redacted] Office phone: [redacted] E-mail: [redacted]
SAE Reporting Information	IQVIA Lifecycle Safety	4820 Emperor Boulevard Durham, NC 27703 E-mail: Sage.Safety@iqvia.com Fax: +1-855-638-1674 SAE Hotline: +1-855-564-2229
Product Complaints	Sage Therapeutics, Inc.	E-mail: productcomplaints@sagerx.com Phone: +1-833-554-7243

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics, Inc. (hereafter referred to as Sage Therapeutics, or Sage)

Name of Investigational Product:
SAGE-324 Oral Tablet

Name of Active Ingredient:
SAGE-324

Title of Study:
A Phase 2, Double-blind, Placebo-controlled, Randomized Study Evaluating the Efficacy, Safety, and Tolerability of SAGE-324 Monotherapy and Adjunctive Therapy with Propranolol in the Treatment of Individuals with Essential Tremor

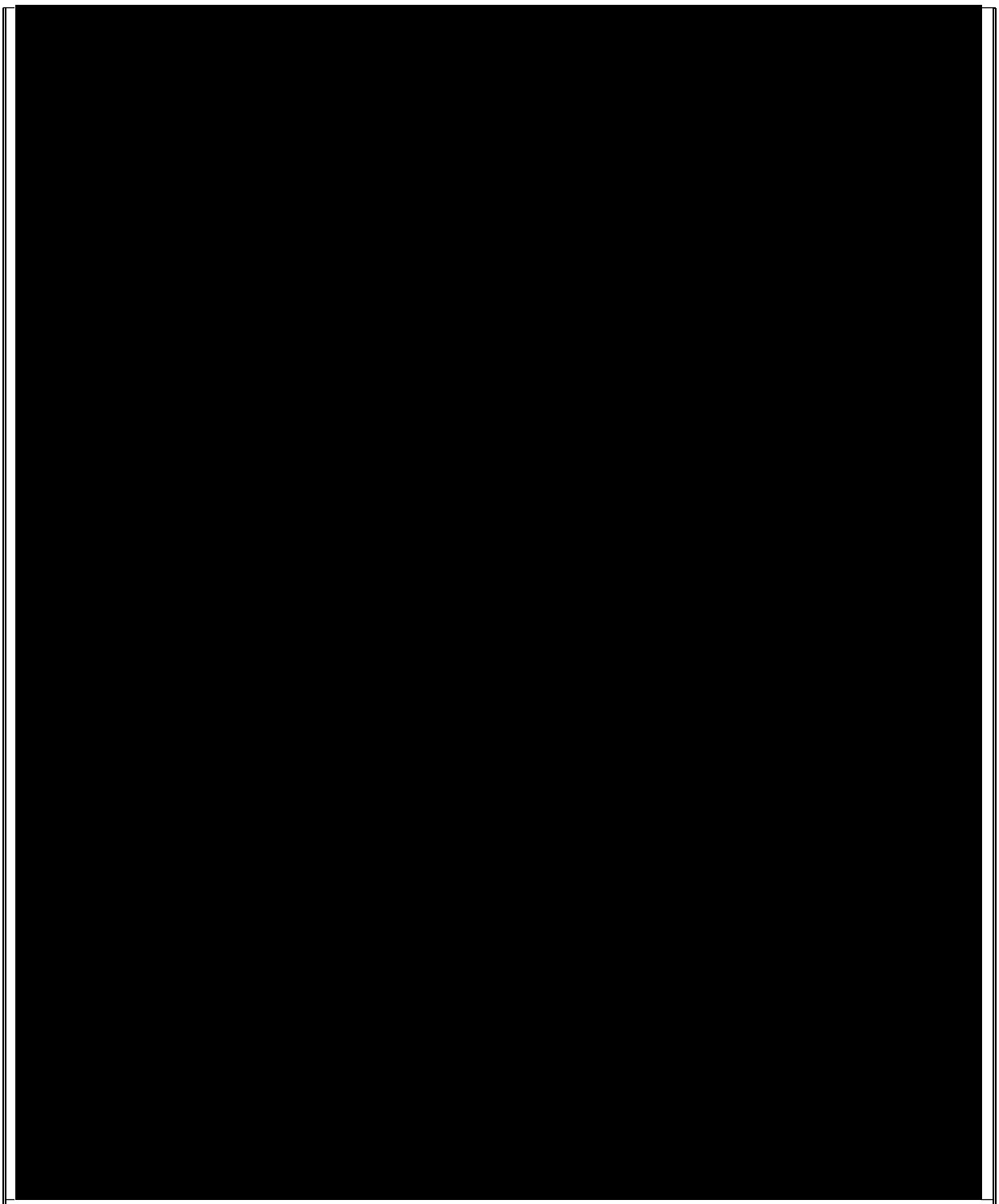
Number of Sites and Study Location: This study will take place at approximately 30 sites in the United States.

Phase of Development: Phase 2

Planned Duration for each Study Participant:
The duration of participation (from Screening through the final follow-up visit) for each participant is estimated to be up to 72 days.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the effect of SAGE-324 compared to placebo on tremor reduction in individuals with essential tremor (ET)	Change from baseline compared to placebo in Kinesia ONE™ accelerometer scores after 28 days of treatment
Secondary	
• To assess the effect of SAGE-324 compared to placebo on activities of daily living (ADLs), total performance, and upper extremities	• Change from baseline compared to placebo in Kinesia ONE accelerometer scores at all other timepoints • Change from baseline compared to placebo in the following: - The Essential Tremor Rating Assessment (TETRAS) Scale ADL score - TETRAS total performance score - TETRAS performance subscale part 4 upper limb tremor score
• To evaluate the safety and tolerability of SAGE-324	• Incidence of treatment-emergent adverse events (TEAEs)



Study Description:

This is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of SAGE-324 as monotherapy and adjunctive therapy with propranolol in individuals with ET. Participants, site staff, and sponsor personnel will be masked to treatment allocation.

This study includes a Screening Period of up to 28 days, a 29-day treatment period (28 days of dosing), and a 14-day follow up period. After providing informed consent, participants will undergo screening assessments as outlined in Table 2 to determine eligibility.

Screening Period: The Screening Period begins with the signing of the informed consent form (ICF). Following completion of screening, on Day 1, eligible participants will visit the study center and will be randomized to 1 of 2 treatment groups (SAGE-324 60 mg daily, or placebo) in a 1:1 ratio. Randomization will be stratified based on the use of propranolol for the treatment of ET (Y/N). Participants who are on a propranolol regimen must have been on a stable dose for at least 1 month prior to Day 1 and will continue to be on a stable dose during the Treatment Period. Participants will complete baseline assessments of safety and efficacy, including the clinician-rated TETRAS and quantitative Kinesia ONE assessments of tremor, as specified in the Schedule of Assessments (Table 2).

Double-Blind Treatment Period: Starting on Day 1, participants will receive a single dose of investigational product (IP) once daily for 28 days on an outpatient basis. Doses occurring on scheduled clinic visits will be administered in the clinic, and doses occurring on all other days may be self-administered by the participant at home during the 29-day Treatment Period (28 days of dosing). During the Treatment Period, participants will return to the study center approximately once per week for efficacy and safety assessments as specified in Table 2. Participants will be trained on the use of software applications and devices necessary to complete questionnaires or other assessments as required.

Follow Up Period: Follow up visits will be conducted on an outpatient basis. Participants will continue to complete questionnaires as indicated in Table 2 and will receive a phone call approximately 7 days after the last dose of IP (ie, Day 35) for safety monitoring. Participants will return to the study center for an end of study visit approximately 14 days following the last dose of IP (ie, Day 42).

Participants who discontinue IP during the Treatment Period will be asked to return to the clinic as soon as possible for an end of treatment (EOT) visit. Follow-up visits should take place as scheduled, or relative to the last dose of IP if discontinuing treatment early. If at any time after the EOT visit, a participant decides to withdraw from the study, the participant should return for an early termination visit (ETV). The EOT and ETV can be on the same day if a participant discontinues IP and withdraws from the study on the same day during a clinic visit; in this case, all events scheduled for the EOT visit will be conducted.

During the study, a phone call will be conducted once per week (preferably mid-week) in between clinic visits, to review current status of participant.

Number of Participants (planned): Approximately 60 participants, with approximately 30 per arm.

Eligibility Criteria:

Inclusion Criteria:

1. Participant has signed an ICF before any study-specific procedures or washout of drugs is performed.
2. Participant is 18 to 80 years of age, inclusive, at the time informed consent is obtained.
3. Participant has a diagnosis of ET, as defined by all of the following criteria:
    a. Isolated tremor syndrome consisting of bilateral upper limb action tremor
    b. At least 3 years duration
    c. With or without tremor in other locations (eg, head, voice, or lower limbs)
    d. Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism, isolated focal tremors (eg, voice, head), task- and position-specific tremors, sudden tremor onset or evidence of step-wise deterioration of tremor
4. Participant has a combined total upper extremity TETRAS score of ≥8 with at least 1 upper extremity TETRAS score >4.
5. Participant is willing to discontinue medications taken for the treatment of ET, with the exception of propranolol, within 14 days or 5 half-lives (whichever is longer) prior to receiving IP.
6. Participants taking propranolol for the treatment of ET must be on a stable dose for at least 1 month prior to Day 1 and must be willing to maintain their stable dose through Day 29.
7. Participant is willing to discontinue the use of alcohol and drugs of abuse within at least ≥1 week prior to Day 1 and through Day 29 of the study.
8. Female participant agrees to use at least one method of highly effective contraception as listed in Section 8.2.4 during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does include abstinence).
9. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 13 weeks after receiving study drug, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 8.2.4.
10. Male participant is willing to abstain from sperm donation for the duration of the study and for 13 weeks after receiving study drug.
11. Female participant must have a pregnancy test result that is confirmed as negative at Screening and Day 1.
12. At the discretion of the Investigator, participant is medically stable and ambulatory, and has been on stable dose(s) of any necessary prescription or over the counter medication(s) for at least 30 days prior to Day 1, or changes/discontinues their use prior to Day 1 with the appropriate washout, as applicable per investigator judgement.

13. Participant has no clinically significant findings, as determined by the investigator, on physical examination including mental state examination (MSE) and neurologic examination, 12-lead ECG, or clinical laboratory tests.

Exclusion Criteria:

1. Participant has presence of known causes of enhanced physiological tremor.
2. Participant has had recent exposure (14 days prior to Day 1) to tremorgenic drugs or presence of a drug or alcohol withdrawal state.
3. Participant has had direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor.
4. Participant has had a previous procedure for the treatment of ET, deep brain stimulation, brain lesioning, or magnetic resonance (MR) guided procedure, eg, MR-guided focused ultrasound.
5. Participant has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.)
6. Participant has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic (hypothyroidism with stable thyroid replacement is acceptable), or oncological disease.
7. Participant has 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.
8. Participant has history of alcohol or drug abuse within 6 months prior to Screening, or a positive screen for alcohol on the Day 1 visit, or a positive screen for drugs of abuse at Screening or at the Day 1 visit.
9. Participant has a known allergy to SAGE-324 or any excipient.
10. Participant has had exposure to another investigational drug or device within 30 days prior to the Day 1 visit.
11. Participant has history or suicidal behavior within 2 years or answers “YES” to questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk or suicide in the opinion of the investigator
12. Participant has donated one or more units (1 unit = 450 mL) of blood or experienced acute loss of an equivalent amount of blood within 60 days prior to Day 1.
13. Participant is unable to perform Kinesia ONE assessments or unable to use the device required to perform the assessment.
14. Participant has any condition or comorbidity that in the opinion of the investigator would limit or interfere with the participant’s ability to complete or partake in the study.
15. Participant is unwilling or unable to comply with study procedures and required training.
16. Participant has used any known moderate or strong cytochrome P450 3A4 or P450 2D6 inhibitors and/or inducers within 14 days or 5 half-lives (whichever is longer) prior to Day 1 or consumed grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St.

John's Wort or products containing these within 30 days prior to Day 1. Use of mild cytochrome inhibitors and/or inducers may be permitted.

17. Participant has concurrent or recent exposure (14 days prior to the Day 1 visit) to sedative/hypnotic drugs, stimulants, eg, opioids, highly-caffeinated beverages or dietary supplements containing high doses of caffeine, or recent increase above regular daily consumption of coffee.
18. Participant has concurrent or recent exposure (30 days prior to the Day 1 visit) to long-acting benzodiazepines.
19. Participant plans to undergo elective surgery or relocate during participation in the study.
20. Participant is investigative site personnel or a member of their immediate families (spouse, parent, child or sibling whether biological or legally adopted).
21. Participant has a positive urine cotinine screen at Screening or the Day 1 visit.

Investigational Product Dosage and Mode of Administration:

SAGE-324 (60 mg) or matched placebo oral tablets will be administered in the clinic or self-administered once daily, in the morning with food.

Duration of Treatment:

Each participant will receive a single dose of SAGE-324 oral tablets or matching placebo administered once daily for 28 days.

Statistical Methods:

A separate statistical analysis plan (SAP) will provide a detailed description of the data analyses to be performed in the study. The SAP will be finalized and approved prior to database lock.

General Considerations

For the purpose of all efficacy and safety analyses where applicable, baseline is defined as the last measurement prior to the start of IP administration.

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

Analysis Sets

The Randomized Set is defined as all participants who are randomized.

The Safety Set will include all participants who were administered IP.

The Full Analysis Set will include all randomized participants who received any amount of IP and have a baseline and at least one postbaseline clinic-based Kinesia ONE accelerometer score.

[redacted]

The Per Protocol Set will include all participants in the Full Analysis Set without any major protocol deviations that could affect efficacy. The review of major protocol deviations will be completed, and the decision on whether the deviation affects efficacy will be documented before database unblinding.

Determination of Sample Size

The sample size of this study is based on the assumption of a 3 points difference in the change from baseline Kinesia ONE accelerometer scores between SAGE-324 and placebo with a standard deviation of 3.5 points. Under these assumptions, a sample size of 25 evaluable participants per group

would provide 85% power for detecting a placebo-adjusted treatment difference of 3 points in Kinesia accelerometer assuming a 2-sided test at an alpha level of 0.05. By including 2 treatment groups and using a 1:1 randomization, a total of 50 evaluable participants are required. Assuming a nonevaluability rate of 15%, approximately 60 participants will be randomized. Additional participants may be enrolled if the drop-out rate is higher than 15%.

Analysis of Primary Efficacy Endpoint

The estimand for the primary efficacy analysis is the treatment difference between SAGE-324 and placebo in mean change from baseline in clinic-based Kinesia ONE accelerometer scores at Day 29 based on Full Analysis Set. This will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline Kinesia ONE accelerometer score, stratification factor, assessment timepoint, and timepoint-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline clinic visits will be included in the model. The main comparison will be between SAGE-324 and placebo at the 29-day timepoint. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz compound symmetry or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not unstructured, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

Analysis of Secondary Efficacy Endpoints

Similar to those methods described above for the primary endpoint, an MMRM will be used to analyze of the change from baseline in TETRAS total performance scores, TETRAS Performance subscale part 4 upper limb tremor scores and TETRAS ADL scores.

Safety Analysis

Safety and tolerability of study drug will be evaluated by incidence of TEAEs/serious adverse events,

[redacted]

Interim Analysis

The sponsor may conduct an interim analysis. Detailed descriptions of planned data analyses will be provided in a separate interim statistical analysis plan (SAP), if applicable.

Table 2: Schedule of Assessments

Assessment	**Screening**	**Treatment Period**									**Follow-up Period**			
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15 (±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**32 (±1) Phone Call**	**35 Safety Phone Call**	**38 (±1) Phone Call**	**42 (±1) EOS/ ETV[a]**
Informed Consent	X													
Inclusion/Exclusion	X													
Demographics	X													
Medical History	X													
Hepatitis/HIV screen	X													
Pregnancy Test (all women)	X (serum; all women)	X (urine; WOCBP only)				X (urine; WOCBP only)				X (urine; WOCBP only)				X (urine; WOCBP only)
FSH (postmenopausal women only)	X													
Randomization[b]		X												
Drug/alcohol screens	X	X		X		X		X		X				X
Physical examination[c]	X	X		X		X		X		X				X
Neurological examination including MSE[c]	X	X		X		X		X		X				X
Body height	X									X				X
Body weight	X	X		X		X		X		X				X
Vital signs[d]	X	X		X		X		X		X				X
12-Lead ECG[e]	X	X		X		X		X		X				X
Chemistry/hematology/ coagulation/urinalysis	X	X		X		X		X		X				X
[redacted]														

Assessment	**Screening**	**Treatment Period**									**Follow-up Period**			
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15 (±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**32 (±1) Phone Call**	**35 Safety Phone Call**	**38 (±1) Phone Call**	**42 (±1) EOS/ ETV[a]**
[redacted]														
Kinesia[g]	X	X		X		X		X		X				X
Investigational Product Diary training[h]	X													
TETRAS[i]	X	X		X		X		X		X				X
[redacted]														

Assessment	Screening	Treatment Period									Follow-up Period			
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15 (±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**32 (±1) Phone Call**	**35 Safety Phone Call**	**38 (±1) Phone Call**	**42 (±1) EOS/ ETV[a]**
[redacted]														
Patient Perception of Response Burden										X				X
Participant training[j]	X													
Dispense study drug		X		X		X		X						
IP administration		Administered once daily for 28 days								Not applicable				
AEs/SAEs	X													
Prior and concomitant medication and history[k]	X													

Abbreviations: ADL = activities of daily living; AE = adverse event; [redacted]; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; [redacted]; ETV = early termination visit; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; ICF = informed consent form; min = minutes; IP = investigational product; MSE = mental state examination; [redacted]; SAE = serious adverse event; TETRAS = The Essential Tremor Rating Assessment Scale; WOCBP = women of childbearing potential

Note:

- IP doses will be administered in the clinic on Days 1 and 15. On all other days, IP doses may be administered at home.
- A phone call will be performed once, mid-week between clinic visits during the Treatment Period, and once per week during the Follow-Up Period. During the phone call, the current status of the participant will be reviewed, including but not limited to, AE reporting and characterization, IP compliance review, and assessment of general well-being. Days 1, 8, 15, 22, and 29 are clinic visits.
- The suggested order of assessments during clinic visits is: vital signs, Kinesia, TETRAS, ECG, blood sample collection for [redacted] and clinical laboratory assessments, and questionnaires.
- All Day 1 assessments will be performed predose.

[a] Participants who discontinue IP during the treatment period should return to the site for an EOT visit as soon as possible. Participants who discontinue IP will be encouraged to continue on study and complete safety assessments and follow-up visits. Follow-up visits should take place as scheduled relative to the last dose of IP. If at any time after the EOT visit, a participant decides to withdraw from the study, the participant should return for an ETV. The EOT and ETVs

can be on the same day if a participant discontinues IP and withdraws from the study on the same day during a clinic visit. In such case, all procedures scheduled for EOT and ETV will be conducted.

[b] Randomization will occur on Day 1 only. In addition to meeting all other eligibility criteria, eligibility is determined based on the total upper extremity TETRAS score of ≥8 with at least 1 upper extremity TETRAS score >4 at Screening.

[c] Complete physical examinations (including MSE and neurologic examination as parts of physical examination) should be performed as specified and as clinically necessary (see Section 11.1.3).

[d] Vital signs without orthostatic blood pressure and heart rate will be collected predose in the beginning of each visit and again prior to departing the clinic, at approximately 5 hours (±30 min). Postdose vital signs to include orthostatic blood pressure and heart rate, measured after the participant has been in the supine position for at least 5 minutes and then repeated 1 minute and 3 minutes after standing.

[e] ECGs will be collected and read centrally. ECGs will be performed approximately 5 hours (±30 min) postdose. All ECGs must be performed after the participant has been in a supine position for at least 5 minutes.

[redacted]

[g] Kinesia ONE will be assessed simultaneous to TETRAS Performance subscale part 4 upper limb tremor. On clinic dosing days, participants will perform Kinesia ONE assessments approximately 30 to 60 minutes prior to dosing in the morning. In addition, on Day 15, Kinesia ONE assessments will be performed at 5 and 8 hours (±30 min) postdose.

[h] Training specific to the Investigational Product Diary will be performed prior to randomization.

[i] The TETRAS Performance and TETRAS ADL subscales will be assessed at Screening and predose at each clinic visit postrandomization. The TETRAS Performance subscale part 4 upper limb tremor will be assessed simultaneous to Kinesia ONE. In addition, on Day 15, the TETRAS Performance subscale will be assessed at 5 and 8 hours (±30 min) postdose. Eligibility is determined based on the combined TETRAS performance subscale part 4 upper limb tremor total score ≥8, with at least 1 upper limb score >4 at Screening.

[j] Participants will be trained on the use of software applications and devices necessary for the conduct of the study by site personnel.

[k] Prior and concomitant medications will be recorded during Screening and will include all medications and supplements taken within the 30 days prior to signing the ICF through the first dose of IP. Concomitant medications will be recorded thereafter throughout the duration of the study. At Screening, this will include year of diagnosis and history of treatments for ET since year of diagnosis and use of antidepressant medications taken in the prior 12 months.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ADL	activities of daily living
AUC_{inf}	area under the curve from 0 to infinity
$AUC_{0\text{-}tau}$	area under the concentration-time curve from 0 to end of the dosing period
BMI	body mass index
[redacted]	[redacted]
C_{max}	maximum observed concentration
CRO	contract research organization
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End-of-Study
[redacted]	[redacted]
[redacted]	[redacted]
ET	essential tremor
[redacted]	[redacted]
ETV	early termination visit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
[redacted]	[redacted]
PI	principal investigator
PK	pharmacokinetic
[redacted]	[redacted]

Abbreviation	Definition
[redacted]	[redacted]
PV	pharmacovigilance
QTcF	QT corrected according to Fridericia's formula
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
t_{max}	time of occurrence of C_{max}
WHO	World Health Organization

5. INTRODUCTION

SAGE-324 is a positive allosteric modulator (PAM) of A-type γ-aminobutyric acid-gated chloride channel ($GABA_A$) receptors, the major class of inhibitory neurotransmitter receptors in the brain. In addition to being developed as an adjunctive therapy in epilepsy and other seizure disorders under IND 139201, SAGE-324 is also being developed for the treatment of Essential Tremor (ET).

Essential tremor is a permanently debilitating, neurologically determined, common movement disorder characterized by involuntary rhythmic oscillation of a body part due to intermittent muscle contractions typically occurring when not at rest, thus interfering with fine motor skills associated with daily activities (Olanow 2008, Deuschl 2011, Hopfner 2016, NIH 2019). Although the pathophysiology and etiology of ET is not fully understood, it is postulated that approximately 50% of ET patients feature an autosomal dominant pattern of familial inheritance and that non-inherited cases may have toxin-based or other causality (Olanow 2008, Hopfner 2016). ET is the most common movement disorder in the US, with prevalence estimated to be approximately 2.2% of the population, representing a substantial societal medical burden with over an estimated 7 million ET patients in the US alone (Louis 2014).

In general, active tasks of daily life are adversely impacted by ET, including but not limited to speech, handwriting, household tasks, and occupational demands, contributing negatively to psychosocial well-being, general anxiety, and overall quality of life (Koller, 1989). Although benign in term of its effect on life expectancy, ET is a progressive neurodegenerative condition whose symptoms are typically disabling, often forcing patients to change jobs or seek early retirement (Zappia, 2013). In some cases, serious disability may ensue.

The pharmacological profile of SAGE-324 is theorized to induce therapeutic effect in the treatment of ET. Based on preclinical studies of SAGE-324, which features a different mechanism of action than that of propranolol, the pharmacokinetic (PK)/ pharmacodynamic (PD) profile suggests SAGE-324 may safely ameliorate symptoms in patients suffering from ET, regardless of propranolol use.

There are currently ongoing Phase 1 clinical studies of SAGE-324 in healthy adults and in adults with ET. These studies, in addition to preclinical studies of SAGE-324, are detailed in the investigator's brochure.

With a $GABA_A$ receptor-based mechanism of action featuring positive allosteric modulation capability, SAGE-324 represents a novel approach to treatment of ET with possible utility as monotherapy or adjunctive to propranolol, which may help address the unmet medical need of the ET population, warranting further study of SAGE-324 as a potential treatment for this common movement disorder.

Henceforth, this double-blind, placebo-controlled efficacy and safety study of SAGE-324 will be conducted in adults with and without concomitant use of propranolol and is designed to assess the effect of SAGE-324 on a variety of outcome measures specific to ET disease characteristics and associated quality of life domains.

5.1. Dose Justification

The dose of SAGE-324 planned for this study is 60 mg given as oral tablets, to be administered once daily in the morning with food. The dose was selected based on preliminary data from 3 active studies of SAGE-324, which included: unblinded data from completed cohorts in 324-CLP-101 Part A (oral solution SAGE-324 doses of 3 mg, 10 mg, 30 mg, 45 mg, 60 mg); Part C (oral solution SAGE-324 doses of 30 mg); Part D (oral suspension SAGE-324 doses of 30 mg) in healthy subjects; and preliminary data from open-label Part E (oral suspension SAGE-324 doses of 45 mg and 60 mg) in participants with ET; additional preliminary data from 324-CLP-102 cohorts 1 through 6 (cohorts 1 to 5 unblinded, cohort 6 blinded), which evaluated oral suspension doses ranging from 5 mg to 60 mg; and preliminary unblinded data from 324-CLP-104, which compared the relative bioavailability of the oral tablet (30 mg) vs oral suspension (30 mg) formulations of SAGE-324 and separately the effect of food on the PK of the SAGE-324 oral tablet. In 324-CLP-101 and 324-CLP-102 studies, doses were administered in a fasted state. The preliminary data from all of these active studies collectively informed the route of administration (oral) and dose strength of 60 mg as oral tablets planned for further evaluation in this study.

SAGE-324 was generally well-tolerated in participants with ET and in healthy volunteers, as was shown in the preliminary data of 324-CLP-101 Part E at single administration doses of 45 mg and 60 mg, and in 324-CLP-102 through once-daily administered doses of up to 60 mg for 14 days. In addition, tremor reduction was observed at both doses on TETRAS and Kinesia accelerometry, with greater improvement seen at 60 mg compared to 45 mg.

In the clinically complete study 324-CLP-104, preliminary data showed that SAGE-324 oral tablets, when coadministered with a meal, resulted in exposures approximately equivalent to that of SAGE-324 oral suspension under fasted conditions. Therefore, the SAGE-324 oral tablets are recommended to be administered with food.

5.2. Benefit/Risk Assessment

Based on the mechanism of action of SAGE-324 and the results of completed nonclinical studies and preliminary data of currently ongoing clinical studies of SAGE-324, it is theorized that participants may have symptomatic amelioration, ie, tremor reduction and possibly improved quality of life from potentially stabilizing disease characteristics associated with ET.

Potential risks anticipated in this study are based on available data from toxicology studies of SAGE-324 in addition to preliminary data from 3 ongoing, currently active Phase 1 clinical studies of SAGE-324.

As of 20 December 2019, there have been no deaths or SAEs related to IP, and as of 18 October 2019, based on the preliminary clinical data available, there have been no confirmed clinically significant trends in clinical laboratory evaluations, vital signs, or physical examinations. Available preliminary clinical data is summarized in the Investigator's Brochure.

Based on available preliminary clinical data from SAGE-324 active clinical studies, AEs of somnolence and feeling of relaxation are considered adverse drug reactions. In addition to scheduled clinic visits, the current status of study participants will be reviewed via weekly phone calls, in between clinic visits.

6. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the effect of SAGE-324 compared to placebo on tremor reduction in individuals with essential tremor (ET)	• Change from baseline compared to placebo in Kinesia ONE™ accelerometer scores after 28 days of treatment
Secondary	
• To assess the effect of SAGE-324 compared to placebo on activities of daily living (ADLs), total performance, and upper extremities	• Change from baseline compared to placebo in Kinesia ONE accelerometer scores at all other timepoints • Change from baseline compared to placebo in the following: - The Essential Tremor Rating Assessment (TETRAS) Scale ADL score - TETRAS Total Performance Score - TETRAS Performance Subscale Part 4 Upper Limb Tremor
• To evaluate the safety and tolerability of SAGE-324	• Incidence of treatment-emergent adverse events (TEAEs)
[redacted]	

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of SAGE-324 as monotherapy and adjunctive therapy with propranolol in individuals with ET. Participants, site staff, and sponsor personnel will be masked to treatment allocation (see Section 8.5).

This study includes a Screening Period of up to 28 days, a 29-day treatment period consisting of 28 days of dosing with the end of treatment visit intended to be on Day 29 at trough, and a 14-day follow-up period relative to final dose (Figure 1). After providing informed consent, participants will undergo screening assessments as outlined in Table 2 to determine eligibility.

The Screening Period begins with the signing of the informed consent form (ICF). Following completion of screening, on Day 1, eligible participants will visit the study center and will be randomized to 1 of 2 treatment groups (SAGE-324 60 mg or placebo) in a 1:1 ratio. Randomization will be stratified based on the use of propranolol for the treatment of ET (Y/N). Participants who are on a propranolol regimen must have been on a stable regimen for at least 1 month prior to Day 1 and will continue to be on that stable regimen during the Treatment Period. Participants will complete baseline assessments of safety and efficacy, including the clinician-rated TETRAS and quantitative Kinesia ONE assessments of tremor, as specified in the Schedule of Assessments (Table 2).

During the double-blind Treatment Period, starting on Day 1, participants will receive a single dose of investigational product (IP) once daily for 28 days on an outpatient basis. Doses occurring on scheduled clinic visits will be administered in the clinic, and doses occurring on all other days will be self-administered by the participant at home as specified in Table 2. During the Treatment Period, participants will return to the study center approximately once per week for efficacy and safety assessments as specified in Table 2. In addition, a phone call will be conducted once per week (preferably mid-week) in between clinic visits, to review current status of the participant.

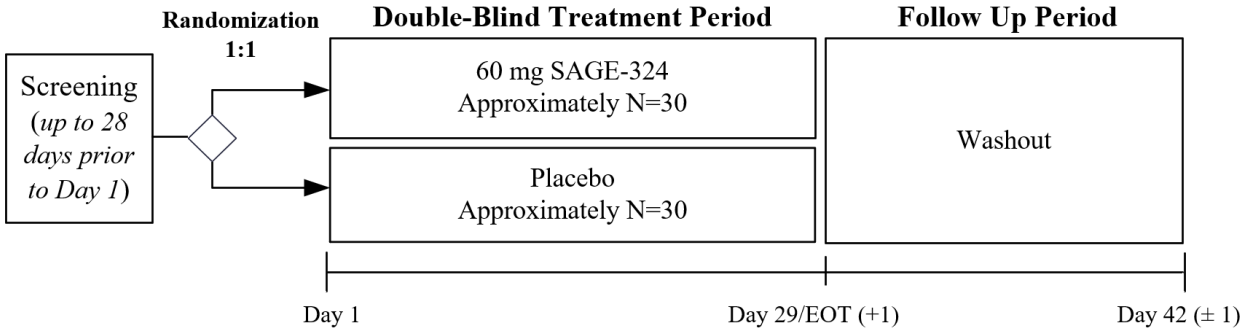
In addition to Kinesia ONE-specific training, clinical study center staff and study participants will be trained on the use of software applications and devices necessary to complete questionnaires or other assessments as required. During in-clinic visits, clinical study center staff will be available to assist participants as needed, to ensure they can access and use the software applications and devices correctly according to the training.

During the follow-up period, visits will be conducted on an outpatient basis. In addition to the phone calls to review current status, participants will receive a phone call approximately 7 days after the last dose of IP (ie, Day 35) for safety monitoring. Participants will return to the study center for an end of study visit approximately 14 days following the last dose of IP (ie, Day 42).

Participants who discontinue IP during the Treatment Period will be asked to return to the clinic as soon as possible for an end of treatment (EOT) visit. Follow-up visits should take place as scheduled, or relative to the last dose of IP if discontinuing treatment early. If at any time after the EOT visit, a participant decides to withdraw from the study, the participant should return for an early termination visit (ETV). The EOT and ETV can be on the same day if a participant

discontinues IP and withdraws from the study on the same day during a clinic visit; in this case, all events scheduled for the EOT visit will be conducted.

Figure 1: Study Design



Abbreviation: EOT = end of treatment

7.2. Number of Participants

Approximately 60 participants are planned, with approximately 30 participants enrolled per arm, to produce 25 evaluable participants per arm for primary efficacy analysis. Additional participants may be randomized if the drop-out rate is higher than anticipated (ie, >15%).

7.3. Treatment Assignment

Participants will be assigned to IP (active or placebo) in accordance with the randomization schedule on Day 1. Additional details on randomization and blinding are provided in Section 8.5.

7.4. Dose Adjustment Criteria

If participants report adverse events that are considered by the investigator to be related to the IP and not tolerable, the investigator may reduce the dose of IP from 60 mg in 15 mg increments until tolerability is established. The reduced dose of IP will continue to be administered once daily at the same schedule as specified in the Schedule of Assessments (Table 2). The dose of IP may not be increased for the remainder of the study. The dose may not be reduced below 30 mg: if intolerable adverse events persist at the 30 mg dose, the IP should be permanently stopped.

Otherwise, IP doses will not be further adjusted for this study except as clinically necessary, eg, interrupting dose due to an AE or serious adverse event (SAE) considered related to IP.

7.5. Criteria for Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to participants, 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 IRB/ethics committee (EC), where required, and initiate withdrawal procedures for participating participants.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

Participants must meet all of the following criteria to qualify for participation in this study:

1. Participant has signed an ICF before any study-specific procedures or washout of drugs is performed.
2. Participant is 18 to 80 years of age, inclusive, at the time informed consent is obtained.
3. Participant has a diagnosis of ET, as defined by all of the following criteria:
    a. Isolated tremor syndrome consisting of bilateral upper limb action tremor
    b. At least 3 years duration
    c. With or without tremor in other locations (eg, head, voice, or lower limbs)
    d. Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism, isolated focal tremors (eg, voice, head), task- and position-specific tremors, sudden tremor onset or evidence of step-wise deterioration of tremor
4. Participant has a combined total upper extremity TETRAS score of ≥8 with at least 1 upper extremity TETRAS score >4.
5. Participant is willing to discontinue medications taken for the treatment of ET, with the exception of propranolol, within 14 days or 5 half-lives (whichever is longer) prior to receiving IP.
6. Participants taking propranolol for the treatment of ET must be on a stable dose for at least 1 month prior to Day 1 and must be willing to maintain their stable dose through Day 29.
7. Participant is willing to discontinue the use of alcohol and drugs of abuse within at least ≥1 week prior to Day 1 and through Day 29 of the study.
8. Female participant agrees to use at least one method of highly effective contraception as listed in Section 8.2.4 during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does include abstinence).
9. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 13 weeks after receiving study drug, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 8.2.4.
10. Male participant is willing to abstain from sperm donation for the duration of the study and for 13 weeks after receiving study drug.
11. Female participant must have a pregnancy test result that is confirmed as negative at Screening and Day 1.

12. At the discretion of the investigator, participant is medically stable and ambulatory, and is on stable dose(s) of any necessary prescription or over-the-counter medication(s) for at least 30 Days prior to Day 1, or changes/discontinues their use prior to Day 1 with the appropriate washout, as applicable per investigator judgement.
13. Participant has no clinically significant findings, as determined by the investigator, on physical examination including mental state examination (MSE) and neurologic examination, 12-lead ECG, or clinical laboratory tests.

8.2. Participant Exclusion Criteria

Participants who meet any of the following criteria are disqualified from participation in this study:

1. Participant has presence of known causes of enhanced physiological tremor.
2. Participant has had recent exposure (14 days prior to Day 1) to tremorgenic drugs or presence of a drug or alcohol withdrawal state.
3. Participant has had direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor.
4. Participant has had a previous procedure for the treatment of ET, deep brain stimulation, brain lesioning, or magnetic resonance (MR) guided procedure, eg, MR-guided focused ultrasound.
5. Participant has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.)
6. Participant has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic (hypothyroidism with stable thyroid replacement is acceptable), or oncological disease.
7. Participant has 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.
8. Participant has history of alcohol or drug abuse within 6 months prior to Screening, or a positive screen for alcohol on the Day 1 visit, or a positive screen for drugs of abuse at Screening or at the Day 1 visit.
9. Participant has a known allergy to SAGE-324 or any excipient.
10. Participant has had exposure to another investigational drug or device within 30 days prior to the Day 1 visit.
11. Participant has history or suicidal behavior within 2 years or answers “YES” to questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk or suicide in the opinion of the investigator
12. Participant has donated one or more units (1 unit = 450 mL) of blood or experienced acute loss of an equivalent amount of blood within 60 days prior to Day 1.

13. Participant is unable to perform Kinesia ONE assessments or unable to use the device required to perform the assessment.
14. Participant has any condition or comorbidity that in the opinion of the investigator would limit or interfere with the participant's ability to complete or partake in the study.
15. Participant is unwilling or unable to comply with study procedures and required training.
16. Participant has used any known moderate or strong cytochrome P450 3A4 or P450 2D6 inhibitors and/or inducers within 14 days or 5 half-lives (whichever is longer) prior to Day 1 or consumed grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St. John's Wort or products containing these within 30 days prior to Day 1. Use of mild cytochrome inhibitors and/or inducers may be permitted.
17. Participant has concurrent or recent exposure (14 days prior to the Day 1 visit) to sedative/hypnotic drugs, stimulants, eg, opioids, highly-caffeinated beverages or dietary supplements containing high doses of caffeine, or recent increase above regular daily consumption of coffee.
18. Participant has concurrent or recent exposure (30 days prior to the Day 1 visit) to long-acting benzodiazepines
19. Participant plans to undergo elective surgery or relocate during participation in the study.
20. Participant is investigative site personnel or a member of their immediate families (spouse, parent, child or sibling whether biological or legally adopted).
21. Participant has a positive urine cotinine screen at Screening or the Day 1 visit.

8.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned IP or entered in the study, ie, a participant who does not meet 1 or more of the eligibility criteria after providing consent and prior to randomization (Day 1). A minimal set of screen failure information will be collected, including demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

8.4. Investigational Product Discontinuation and Early Termination from the Study

8.4.1. Investigational Product Discontinuation

A participant may withdraw from the study at any time at his/her own request for any reason. The investigator may discontinue a participant from the study and/or from IP for safety, behavioral, compliance, or administrative reasons. Participants who elect to discontinue IP will be encouraged by the Investigator to remain on study and complete the follow-up safety assessments 14 days after the last dose of study drug, in addition to the EOT visit conducted as specified in the Schedule of Assessments (Table 2).

The reason for IP discontinuation and/or the reason for early termination from the study must be documented in the participant's study record and recorded in the participant's electronic case report form (eCRF).

The investigator must notify the sponsor and/or the medical monitor when a participant stops participation in the study for any reason.

If a participant is persistently noncompliant, the investigator should discuss with the sponsor the potential discontinuation of the participant. Any reasons for unwillingness or inability to adhere to the protocol must be recorded in the participant's eCRF, including:

- missed visits;
- interruptions in the schedule of study drug administration;
- non-permitted medications

Participants who discontinue IP due to an AE, regardless of investigator-determined causality, should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant.

8.4.2. Early Termination from the Study

At the time of study withdrawal/stopping study participation, if possible within 48 hours of final IP dose, an EOS/ETV visit should be conducted as specified in the Schedule of Assessments (Table 2). The participant will be permanently discontinued both from the IP and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor will retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

8.4.3. Loss to Follow-up

A participant will be deemed lost to follow-up after 3 attempts at contacting the participant have been unsuccessful.

8.4.4. Replacement of Participants

Participants will not be replaced.

9. TREATMENT OF PARTICIPANTS

9.1. Description of Investigational Product

SAGE-324 is an orally administered tablet provided in 5 mg or 15 mg (when available) dose strengths. Participants will receive IP (60 mg total dose of SAGE-324 tablets, or appearance-matched placebo tablets) according to the randomization schedule. Additional details regarding IP preparation, formulation, and storage are included in Section 9.

9.2. Prior Medications, Concomitant Medications, Restrictions, and Contraception Requirements

9.2.1. Prior and Concomitant Medications and/or Supplements

The start and end dates, route, dose/units, frequency, and indication for all medications and/or supplements taken within 30 days prior to signing the informed consent through the first dose of IP will be recorded. Use of all medications taken within the 30 days prior to Screening will be recorded.

All medications and/or supplements taken from the first dose of IP through the Day 42 (±1 days) visit (including start and end dates route, dose/units, frequency, and indication) will be recorded on the eCRF. Any concomitant medication determined necessary for the welfare of the participant may be given at the discretion of the investigator at any time during the study.

9.2.2. Prohibited Medications

Use or consumption of the following is prohibited for the timeframes specified:

- Treatment with an investigational drug or device during the 30 days or 5 half-lives (if known) of the investigational drug, whichever is longer, prior to Screening or during the study
- Use of any prescription or over-the-counter medication (except for propranolol use as prescribed, and/or up to 3 g/day of acetaminophen), herbal medication, vitamins, or mineral supplements within 14 days prior to first IP administration, or during the study period
- Use of tremorgenic drugs or agents known to affect SAGE-324 drug metabolism (any known CYP450 3A4 inhibitors and/or inducers) within the 28 days or 5 terminal half-lives (whichever is longer) prior to first IP administration or during the study period

9.2.3. Other Restrictions

In addition to alcohol and drugs of abuse, the following are not permitted during the study, or within 14 days of the first IP dose: sedative/hypnotic drugs, stimulants, eg, opioids, benzodiazepines, highly-caffeinated beverages or dietary supplements containing caffeine.

9.2.4. Acceptable Forms of Contraception

Acceptable forms of highly effective contraception for participants of childbearing potential or for partners of male participants who are of childbearing potential include:

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal ligation or bilateral tubal occlusion (performed at least 3 months prior to Screening)
- Vasectomized partner (performed at least 3 months prior to Screening)
- Sexual abstinence (no sexual intercourse)

Acceptable forms of contraception for male participants include:

- Sexual abstinence (no sexual intercourse)
- History of vasectomy (performed at least 3 months prior to Screening)
- Condom with spermicide used together with highly effective female contraceptive methods if the female partner(s) is of childbearing potential (see above for list of acceptable female contraceptive methods)

9.3. Intervention after the End of the Study

There is no planned intervention following the end of the study.

9.4. Treatment Adherence

The first dose of IP will be received and administered by participants in the clinic. Participants will be dispensed a 7-day supply of IP to orally self-administer at home with instructions specifying to administer in the morning with food. Treatment adherence will be monitored by the site staff at each in-clinic visit by direct questioning and counting returned tablets and will be documented. Details on drug accountability are included in Section 9.6.

9.5. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Participants will be randomized in a stratified manner based on propranolol for the treatment of ET (Y/N); randomization will be done within each stratum in a 1:1 ratio to treatment groups (SAGE-324, 60 mg or placebo). Participants, site staff, and the sponsor will be blinded to treatment allocation. Randomization schedules will be generated by an independent statistician. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

9.5.1. Emergency Unblinding

During the study, the blind is to be broken only when the safety of a participant is at risk and the treatment plan is dependent on the study treatment received. Unless a participant is at immediate

risk, the Investigator should make diligent attempts to contact Sage prior to unblinding the study treatment administered to a participant. Requests from the investigator about the treatment administered to study participants should be discussed with the Sage Medical Monitor. If the unblinding occurs without Sage's knowledge, the investigator must notify Sage within 24 hours of breaking the blind. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

In all cases where the IP allocation for a participant is unblinded, pertinent information (including the reason for unblinding) must be documented in the participant's records and on the eCRF. At the time of withdrawal from the study/stopping participation, if possible, an EOT and/or ETV should be conducted.

If a participant or study personnel become unblinded to treatment, the participant will be excluded from the Per Protocol analysis set, as detailed further in the statistical analysis plan.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

Table 3: Investigational Product

	Investigational Product	
Product Name:	SAGE-324	Placebo
Dosage Form:	Tablet	Tablet
Tablet Strength	5 mg, 15 mg	0 mg, appearance-matched to 5 mg, and 15 mg, respectively
Route of Administration	Oral	Oral
Physical Description	Immediate release white to off-white, round, film-coated tablet containing 5 mg or 15 mg of SAGE-324 drug substance, and composed of lactose, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and fumed silica, featuring Opadry® II white as the coating agent.	White to off-white, round, film-coated tablet containing no drug substance, composed of lactose, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and fumed silica, featuring Opadry® II white as the coating agent.
Manufacturer	Sage Therapeutics, Inc.	

10.2. Investigational Product Packaging and Labeling

SAGE-324 Oral Tablets and Placebo Tablets will be packaged in blinded, high density polyethylene (HDPE) containers. The containers used for SAGE-324 and placebo will be identical in appearance. The package labeling conforms to FDA and GMP requirements.

10.3. Investigational Product Storage

Upon receipt of the IP, the investigator, or the responsible pharmacist or designee, will inspect the product and acknowledge receipt in accordance with the study-specific process.

The IP must be carefully stored at the temperature specified in the investigator's brochure, securely and separately from other drugs. The IP may not be used for any purpose other than the present study. Any unused IP must be returned per the sponsor's instructions or destroyed locally per the site's procedure(s). IP may not be destroyed until accountability and reconciliation procedures have been completed and monitored.

The Investigator or designee will be responsible for ensuring appropriate storage, dispensing, inventory, and accountability of the IP. An accurate, timely record of the disposition of the IP must be maintained.

10.4. Investigational Product Preparation

The IP will be in tablet form and provided in blinded packaging. No preparation is required for the tablet, which is administered orally as described below.

10.5. Investigational Product Administration

The IP will be administered in the clinic or at home as specified in the Schedule of Assessments (Table 2). The IP will be provided as tablets, sufficient in number to achieve a dose of 60 mg. IP will be orally administered once daily in the morning, with food.

10.6. Investigational Product Accountability, Handling, and Disposal

Upon receipt of IP, the investigator(s), or the responsible pharmacist or designee, will inspect the IP and complete and follow the instructions regarding receipt and storage in the investigator's brochure and (where applicable) in the Pharmacy Manual. A copy of the shipping documentation will be kept in the study files.

The designated site staff will dispense the supplied participant-specific kits to participants at the planned dispensation visit intervals outlined in the Schedule of Assessments (Table 2).

An interactive response technology (IRT) will be used to capture participant-identifying information. The IRT will be used to randomize the eligible participant into the study and provides the kit number of the IP to be dispensed to that participant.

If dispensing errors or discrepancies are discovered by site staff or sponsor's designee, the sponsor must be notified immediately.

The IP provided is for use only as directed in this protocol. The investigator or designee must keep a record of all IP received, used and returned/discarded.

Sage Therapeutics will be permitted access to the study supplies at any time with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

The investigator, pharmacist, or qualified designee is responsible for drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

At the end of the study, any unused IP tablets will be returned to Sage Therapeutics for destruction or destroyed locally per the site's procedures; disposition of IP will be documented. IP may not be destroyed until accountability and reconciliation procedures have been completed and monitored.

10.7. Product Complaints

A product complaint is any written, electronic, or verbal expression of dissatisfaction regarding the identity, quality, reliability, safety, purity, potency, effectiveness or performance (applicable for approved marketed products) of a drug product after it is released for distribution.

In the course of conduct of the study, study personnel may become aware of a product complaint associated with the use of a Sage product. Personnel shall notify Sage within 24 hours by forwarding the product complaint information via the contact information listed in Table 1 and in the Pharmacy Manual. Where possible, personnel should segregate and retain any product,

materials, or packaging associated with the product complaint until further instruction is provided by Sage or its designated representative(s).

11. EFFICACY ASSESSMENTS AND CLINICAL PHARMACOLOGY ASSESSMENTS

11.1. Efficacy Assessments

11.1.1. Kinesia ONE™ Accelerometer Score

Kinesia ONE™ is an ISO-certified wireless motion sensor worn distally on the index finger, which utilizes 3 orthogonal accelerometers and 3 orthogonal gyroscopes to monitor three-dimensional motion. Data is transmitted wirelessly from the sensor to a Bluetooth technology-enabled device to use with the Kinesia ONE software (eg, Apple iPad or similar device with preinstalled Kinesia ONE software). The device has received FDA clearance.

Via the Kinesia ONE software application, measures of three-dimensional motion are converted to scores ranging from 0 to 4, per assessed maneuver; higher scores indicate greater tremor severity. Motion in both arms is captured.

Participants will complete this assessment at each clinic visit as specified in the Schedule of Assessments (Table 2).

11.1.2. The Essential Tremor Rating Assessment Scale

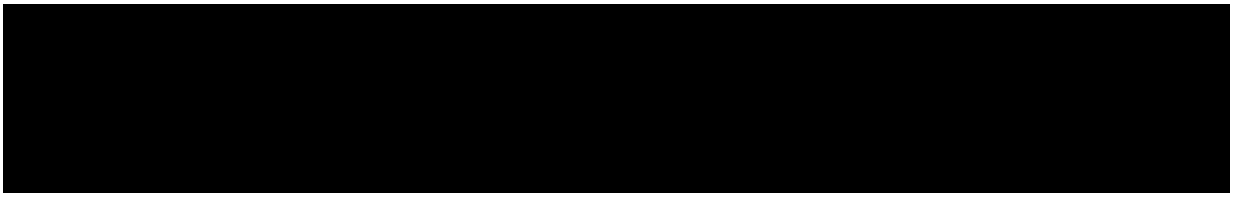
TETRAS is a validated, comprehensive clinical assessment of essential tremor (Elble 2013).

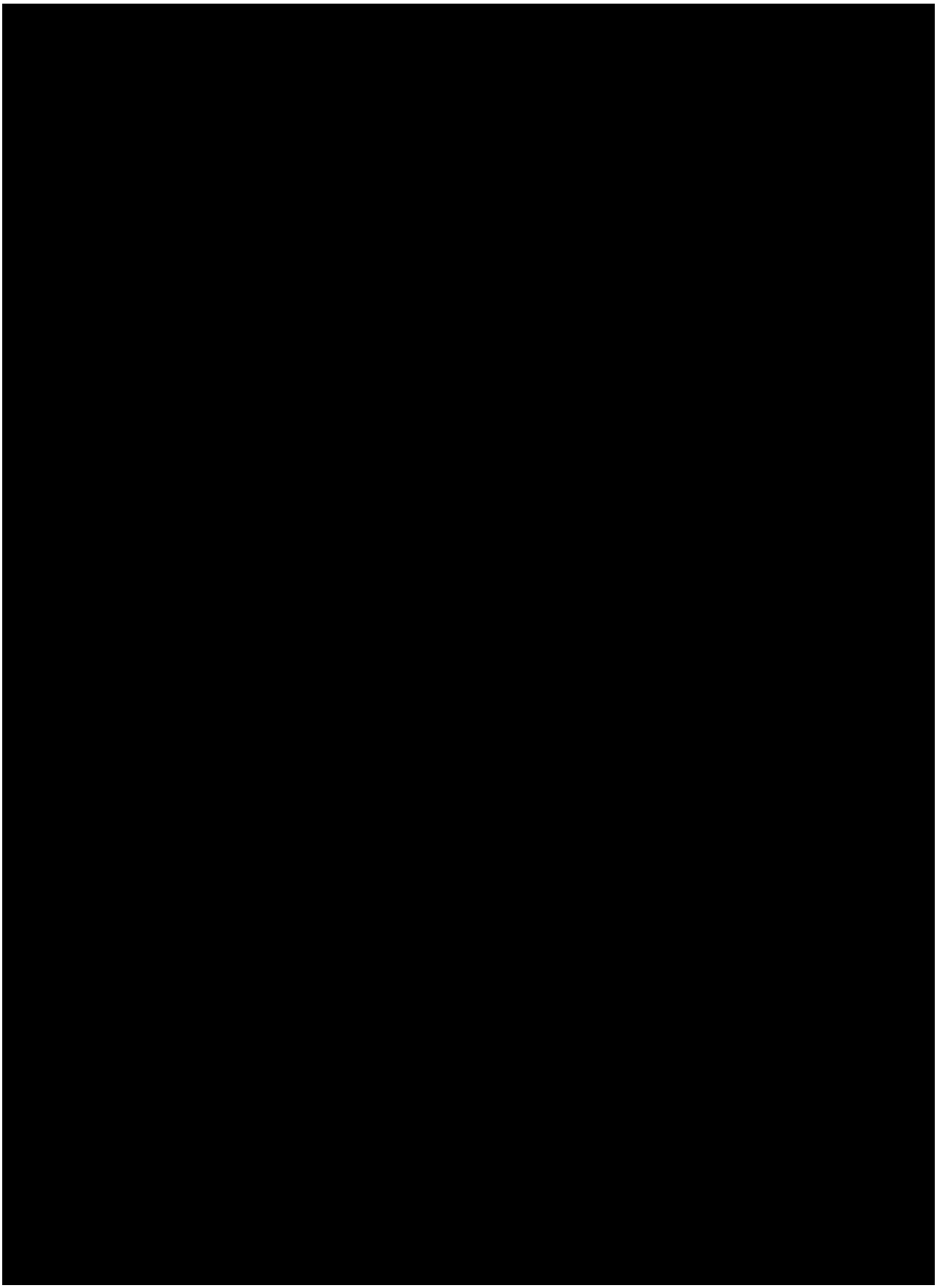
Three different components of TETRAS will be assessed in this study. The TETRAS ADL subscale, total performance score, and performance subscale part 4 upper limb tremor score, and will each be separately assessed at each clinic visit as specified in the Schedule of Assessments (Table 2).

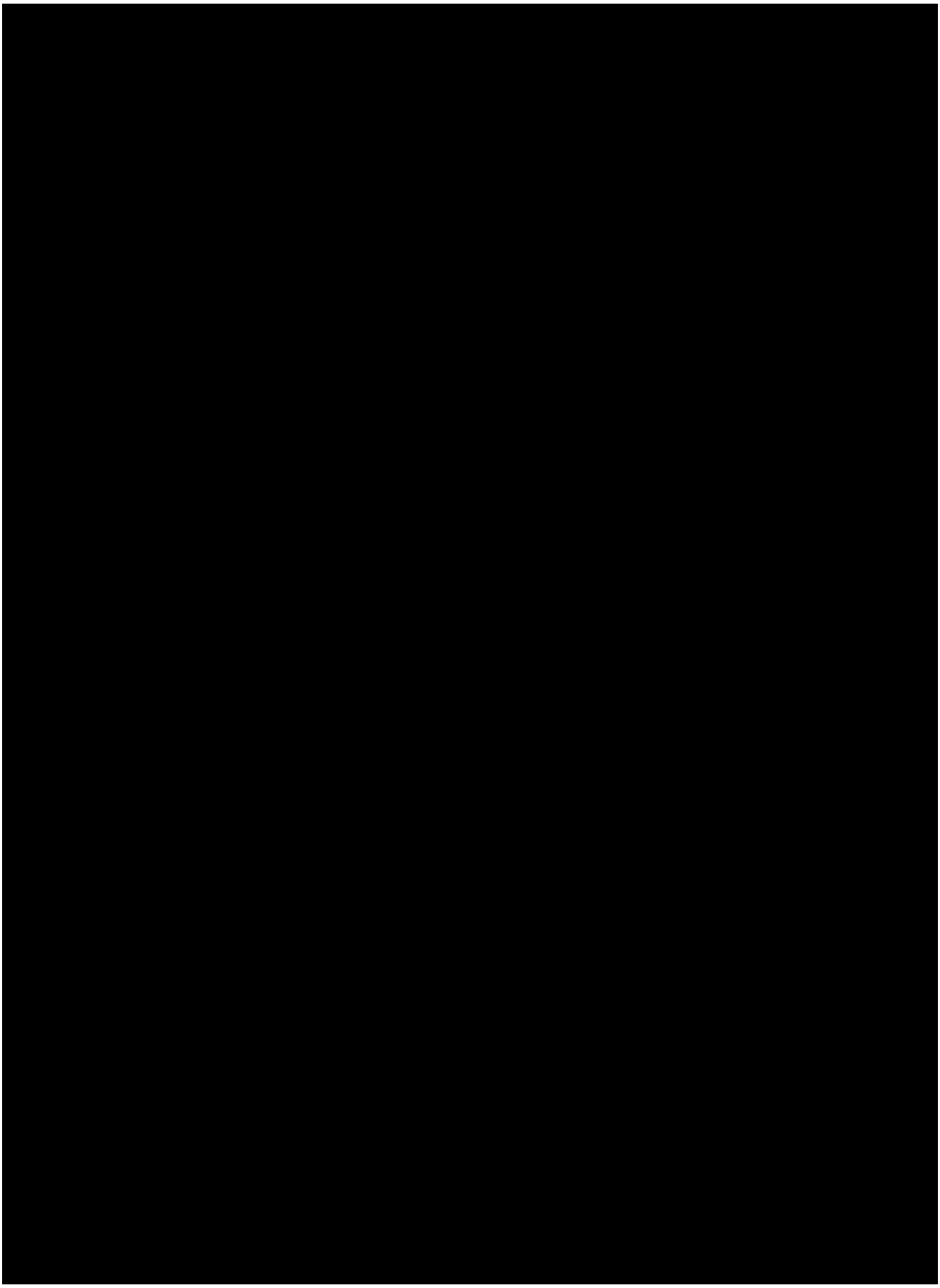
The ADL subscale assesses how ET is impacting typical activities of daily living (ie, speech, eating, drinking, dressing, personal hygiene, writing, occupational impairment, social impact, and activities affected by upper limb tremor). It consists of 12 items that are each rated in from 0 (normal activity) to 4 (severe abnormality). The overall ADL score range is 0 to 48.

The total performance score is based on overall rating of the performance subscale, which measures tremor amplitude in the voice, limbs, head, face, trunk, and also measures functional task capabilities, ie, handwriting, spirography, and holding a pen over a dot. Each of these items is rated on a scale from 0 (no tremor) to 4 (severe tremor). Collectively, the performance items generate an overall performance score from 0 to 64.

For the performance subscale part 4 upper limb tremor score, all 3 maneuvers in the upper limb assessments of part 4 (subscale items 4a, 4b, and 4c) will be completed for both arms, first for the left arm and then for the right. The part 4 subscale ordinally rates postural (limbs extended forward maneuver, and wing-beating [elbows flexed] maneuver), and kinetic (finger-nose-finger maneuver) tremor on a 0 to 4 severity scale in 0.5-point increments.







[redacted]

11.3. Other Patient-Reported Assessments

11.3.1. Patient Perception of Response Burden

The Patient Perception of Response Burden Questionnaire is a patient-reported measure that assesses the multidimensional construct of response burden (Atkinson 2019).

Participants respond to 6 items assessing 1) how well the questions related to their actual concerns, 2) how comfortable the participants were with answering the questions, 3) how well the survey characterized their health and well-being, 4) the length of time to complete the questionnaires, 5) whether questions seemed unimportant or repetitive, and 6) what additional information should have been gathered. Items 1 to 3 are assessed on a 0 to 10 scale, item 4 is assessed on a 1 to 3 scale, and items 5 and 6 are open-ended. Items 1 and 4 are reverse scored. A composite score can be calculated to create a weighted representative index of relevance, comfort, and well-being relative to time to completion (ie, items 1, 2, and 3 were summed and multiplied by item 4) for a range of 0 to 72, with higher scores indicative of elevated endorsed response burden. The open-ended items will be summarized thematically. The Patient Perception of Response Burden Questionnaire will be performed as specified in the Schedule of Assessments (Table 2).

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

All assessments will be conducted according to the Schedule of Assessments (Table 2).

12.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, ethnicity) and a full medical history will be documented. This must also additionally include participant recall of history of ET, disease duration, past treatments used, and responsiveness to alcohol and/or other treatments with use intended as off-label treatment of ET (eg, primidone or similar therapies).

12.1.2. Weight and Height

Height and weight will be measured and documented. Body mass index (BMI) will be calculated and documented.

12.1.3. Physical Examination

Whenever possible, the same individual should perform all physical examinations. Physical examinations will include assessment of body systems (eg, head, eye, ear, nose and throat; heart; lungs; abdomen; and extremities) as well as cognitive and neurological examination and MSE. Unscheduled physical examinations may also be conducted per the Investigator's discretion.

Any abnormality in physical examinations will be interpreted by an investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents.

12.1.4. Vital Signs

Vital signs comprise heart rate, respiratory rate, temperature, and blood pressure. Systolic and diastolic blood pressure are to be measured after the participant has been supine for at least 5 minutes prior to the measurement. When assessed postdose, orthostatic blood pressure and heart rate will also be measured after the participant has been in the supine position for at least 5 minutes and then repeated approximately 1 and 3 minutes after standing.

Any abnormality in vital signs will be interpreted by an Investigator as abnormal, NCS; or abnormal, CS in source documents.

12.1.5. Electrocardiogram

A 12-lead ECG will be performed. The standard intervals (heart rate, PR, QRS, QT, and QTcF) as well as any rhythm abnormalities will be recorded.

Electrocardiograms will be performed after the participant has been resting in a supine position for at least 5 minutes. When ECG measurements coincide with safety assessments, vital signs assessment or blood draws, procedures should be carried out in said order (vital signs, ECG, blood draw).

All abnormal ECGs will be interpreted by an investigator as abnormal, NCS, or abnormal, CS in source documents.

12.1.6. Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected. Analytes to be evaluated are summarized in Table 4.

Table 4: Summary of Clinical Laboratory Analytes

Biochemistry	*Renal Panel*: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate *Hepatic Panel*: albumin, ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, total protein, lactate dehydrogenase, gamma glutamyl transferase *Other*: triglycerides, cholesterol (low density lipoprotein [LDL], high density lipoprotein [HDL]), creatine phosphokinase, thyroid stimulating hormone (TSH)
Coagulation	activated partial thromboplastin time, prothrombin time, and international normalized ratio
Hematology	red blood cell count, hemoglobin, hematocrit, white blood cell count with differential, platelet count, and if red blood count indices are abnormal, reflex red blood cell morphology as indicated
Urinalysis	protein, glucose, pH, blood, leukocytes, leukocyte estrase, urobilinogen, bilirubin, ketones, nitrite
Virus Serology (Screening only)	hepatitis B antigen; hepatitis C antibodies; HIV-1 and -2 antibodies

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, NCS; or abnormal, CS in source documents.

Follicle stimulating hormone testing will be conducted to confirm whether a participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal (Section 8.1).

12.1.6.1. Drugs of Abuse, Alcohol, Cotinine

Separate urine samples for assessment of selected drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, THC, stimulants, and opiates), cotinine, and alcohol will be collected.

12.1.6.2. Pregnancy Screen

A serum pregnancy test will be conducted for all female participants at Screening; a urine pregnancy test will be conducted for all participants of childbearing potential as specified in the Schedule of Assessments (Table 2).

[redacted]

[redacted]

12.1.8. Safety Phone Call

A phone call will be conducted once per week, preferably mid-week in between clinic visits (as specified in Table 2), to collect information about current health status, general well-being, IP compliance, or to gather other pertinent health-related information as per investigator judgement.

12.2. Adverse Events and Serious Adverse Events

12.2.1. Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

A TEAE is defined as an AE with onset after the start of IP, or any worsening of a preexisting medical condition/AE with onset after the start of IP and throughout the study. The term IP includes any Sage IP, a comparator, or a placebo administered in a clinical trial.

Laboratory abnormalities [redacted] are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be clinically significant. Any abnormalities that meet the criteria for an SAE should be reported in an expedited manner. Laboratory abnormalities [redacted] that are clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

All AEs that occur after any participant has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be reported to Sage Therapeutics.

Participants who discontinue the IP due to an AE, regardless of investigator-determined causality, should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant. Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The sponsor or its representative retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.2. Serious Adverse Event (SAE) Definition

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Places the participant at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

An SAE may also be any other medically important event that, in the opinion of the Investigator may jeopardize the participant or may require medical intervention to prevent 1 of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

All SAEs that occur after any participant has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE report form provided by Sage Therapeutics. Any SAE that is ongoing when the participant completes their final study visit, will be followed by the investigator until the event has resolved, stabilized, returned to baseline status, or until the participant dies or is lost to follow up.

A prescheduled or elective procedure or routinely scheduled treatment will not be considered an SAE, even if the participant is hospitalized. The site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or on a waiting list to be scheduled) prior to obtaining the participant's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress, in the opinion of an Investigator, between the participant's consent to participate in the study and at the time of the procedure or treatment.

12.2.3. Definition of Adverse Events of Special Interest

There are no known adverse events of special interest as of the date of signature approval of this clinical protocol.

12.2.4. Relationship to Investigational Product

The investigator must make the determination of relationship to the IP for each AE (not related, related). The following definitions should be considered when evaluating the relationship of AEs and SAEs to the IP.

Not Related	An AE will be considered "not related" to the use of the IP if there is not a reasonable possibility that the event has been caused by the IP. Factors pointing towards this assessment include but are not limited to: the lack of temporal relationship between administration of the IP and the event, the presence of biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE
Related	An AE will be considered "related" to the use of the IP if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point towards this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of alternative explanation for the AE

12.2.5. Recording Adverse Events

AEs spontaneously reported by the participant 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. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, outcome and seriousness (if applicable), and whether or not it caused the participant to discontinue the IP or withdraw early from the study.

Intensity will be assessed according to the following scale:

- Mild: symptom(s) barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s)
- Moderate: symptom(s) of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptom(s) may be needed
- Severe: symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with IP; treatment for symptom(s) may be given and/or participant hospitalized

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 11.2.2. An AE of severe intensity may not necessarily be considered serious.

12.2.6. Reporting Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE(s), the study site must notify Sage or designee within 24 hours of the study site staff becoming aware of the SAE(s). The investigator must complete, sign and date the SAE report form, verify the accuracy of the information recorded on the SAE report form with the corresponding source documents, and send a copy to Sage or designee.

Additional follow-up information, if required or available, should all be sent to Sage or designee within 24 hours of receipt on a follow-up SAE report form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

SAEs occurring after the designated follow up time for the study, should be reported to Sage or designee according to the timelines noted above only if the Investigator considers the SAE related to IP.

Sage, or designee, is responsible for notifying the relevant regulatory authorities of certain events. It is the principal investigator's responsibility to notify the IRB/EC of all SAEs that occur at his or her site. Investigators will also be notified of all suspected unexpected serious adverse reactions (SUSARs) that occur during the clinical study. Each site is responsible for notifying its IRB of all SUSARs.

In addition, appropriate personnel in Sage Drug Safety and Pharmacovigilance or designee will unblind SUSARs for the purpose of regulatory reporting. Sage or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Sage, or designee, will submit SUSARs to investigators in a blinded fashion.

12.3. Pregnancy

If a participant becomes pregnant after the first administration of IP, pregnancy information must be collected and recorded on the pregnancy form and submitted to the sponsor within 24 hours of learning of the pregnancy. Details will be collected for all pregnancies for which conception was likely to have occurred after the start of IP administration until 5 terminal half-lives following the last administration of IP or until the completion of the study whichever is longer. Any pregnancy occurring in that time frame will be followed until delivery or termination of the pregnancy. The investigator will also attempt to collect pregnancy information on any participant's partner who becomes pregnant after the participant has received the first administration of IP. After obtaining the necessary signed informed consent from the pregnant partner directly, the investigator will follow the same pregnancy reporting procedures specified for pregnant participants.

The participant or participant's partner will be followed to determine the outcome of the pregnancy. The outcome of all pregnancies (eg, spontaneous abortion, elective abortion, normal birth) must be followed and documented even if the participant was discontinued from the study. The investigator will collect follow-up information on the participant or participant's partner and the neonate, and the information will be forwarded to Sage or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication. Any complication during pregnancy (eg, anemia, infections, preeclampsia) should be reported as an AE/SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death), the investigator should follow the procedures for reporting an SAE.

12.4. Overdose

An overdose is any dose of study treatment given to a participant or taken by a participant that exceeds more than one extra tablet within 24 hours as described in protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded.

13. STATISTICS

Detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock. Any changes or additions to the SAP following database lock will be described in detail in the clinical study report.

13.1. Data Analysis Sets

The Randomized Set will include all participants who are randomized.

The Safety Set will include all participants administered IP.

The Full Analysis Set will include all randomized participants who received any amount of IP and have a baseline and at least one postbaseline Kinesia ONE accelerometer score.

[redacted]

The Per Protocol Set will include all participants in the Full Analysis Set without any major protocol deviations that could affect efficacy. The review of major protocol deviations will be completed, and the decision on whether the deviation affects efficacy will be documented before database unblinding.

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All participants will be used in the analyses, as per the analysis populations, using all nonmissing data available. No imputation process will be used to estimate missing data.

13.3. General Considerations

All participant data, including those that are derived, that support the tables and figures will be presented in the participant data listings. Some data may be presented only in participant data listing, some may be presented with a corresponding table or figure; these will be indicated in relevant sections below. Participants will be summarized according to treatment received.

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to receipt of IP.

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

13.4. Demographics and Baseline Characteristics

Demographic data, such as age, race, and ethnicity, and baseline characteristics, such as height, weight, and BMI, will be summarized using the Safety Set.

Pregnancy test results and drug screen results will be listed but not summarized.

Medical history will be listed by participant.

13.5. Efficacy Analysis

The estimand for the primary efficacy analysis is the treatment difference between SAGE-324 and placebo in mean change from baseline in clinic-based Kinesia ONE accelerometer scores at Day 29 based on the Full Analysis Set. This will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline Kinesia ONE accelerometer score, stratification factor, assessment timepoint, and timepoint-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline clinic visits will be included in the model. The main comparison will be between SAGE-324 and placebo at the 29-day timepoint. Model-based point estimates (ie, least squares means, 5% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz compound symmetry or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not UN, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

Similar to those methods described above for the primary endpoint, an MMRM will be used for the analysis of the change from baseline in TETRAS total performance scores, TETRAS performance subscale part 4 upper limb tremor scores and TETRAS ADL scores.

Other efficacy analyses will be specified in the SAP. In general, data will be analyzed using appropriate descriptive statistics or prespecified statistical methods as applicable; participant listings will be provided for all efficacy data. Participants will be analyzed according to randomized treatment for the purpose of efficacy unless otherwise specified.

Sensitivity analyses will be described in the SAP.

13.6. Safety Analyses

Safety and tolerability of SAGE-324 will be evaluated by AEs, concomitant medication usage, [redacted] Safety data will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Set using treatment received.

13.6.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or higher. A treatment-emergent adverse event (TEAE) is defined as an AE with onset after the first dose of IP. The analysis of AEs will be based on the concept of TEAEs. The incidence of TEAEs will be summarized by System Organ Class (SOC) and preferred term. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to IP.

Any TEAEs leading to discontinuation of treatment or withdrawal from the study and any treatment-emergent SAEs will be summarized.

All AEs and SAEs (including those with onset or worsening before the start of IP) through the end of the study will be listed.

[redacted]

13.6.3. Physical Examinations

The occurrence of a physical examination, including MSE, (yes/no) and the date performed will be listed by participant.

[redacted]

13.6.6. 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 (WHO-DD) September 2015, or later.

All medications taken within 30 days prior to informed consent through the duration of the study will be recorded. In addition, all psychotropic medications taken in the previous 30 days prior to screening will be recorded. Those medications taken prior to the initiation of the start of IP will be denoted “Prior”. Those medications taken prior to the initiation of the IP and continuing beyond the initiation of the IP or those medications started at the same time or after the initiation of the IP will be denoted “Concomitant”.

Medications will be presented according to whether they are “Prior” or “Concomitant” as defined above. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Details of prior and concomitant medications will be listed by participant, start date, and verbatim term.

[redacted]

13.8. Sample Size and Power

The sample size of this study is based on the assumption of a 3 points difference in the change from baseline Kinesia ONE accelerometer between SAGE-324 and placebo with a standard deviation of 3.5 points. Under these assumptions, a sample size of 25 evaluable participants per group would provide 85% power for detecting a placebo-adjusted treatment difference of 3 points in Kinesia accelerometer assuming a 2-sided test at an alpha level of 0.05. By including 2 treatment groups and using a 1:1 randomization, a total of 50 evaluable participants are required. Assuming a nonevaluability rate of 15%, approximately 60 participants will be randomized. Additional participants may be enrolled if the dropout rate is greater than 15%.

13.8.1. Interim and Data Monitoring Committee (DMC) Analyses

13.8.1.1. Interim Analysis

The sponsor may conduct an interim analysis. Detailed descriptions of planned data analyses will be provided in a separate interim statistical analysis plan (SAP), if applicable.

13.8.1.2. DMC Analysis

Not applicable

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Sage Therapeutics will visit the investigational study site per Sage SOPs to:

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

During the study, a monitor from Sage Therapeutics or representative 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 case report forms, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the participant'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 participant (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or EC.

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

14.2. Audits and Inspections

Sage Therapeutics or authorized representatives of Sage Therapeutics, a regulatory authority, or an independent EC or an IRB may visit the site to perform an audit(s) or inspection(s), including source data verification. The purpose of a Sage Therapeutics audit or a regulatory authority 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/ICH GCP guidelines, and any applicable regulatory requirements. The Investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency or IRB/EC about an inspection.

14.3. Institutional Review Board or Ethics Committee

The principal investigator must obtain IRB (or EC) approval for the clinical study prior to enrolling a participant. Initial IRB (or EC) approval, and all materials approved by the IRB (or EC) for this study including the participant consent form and recruitment materials must be maintained by the investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practice and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit(s) at the clinical site. Please see Section 13.2 for more details regarding the audit process.

The Investigator must have adequate quality control practices to ensure that the study is performed in a manner consistent with the protocol, GCP/ICH GCP guidelines, and applicable regulatory requirements. The investigator is responsible for reviewing all identified protocol deviations. Significant protocol deviations should be reported to the IRB/EC per the IRB/EC's written procedures.

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. When the investigator retains the services of any individual or party to perform trial-related duties and functions, the Investigator must ensure the individual or party is qualified to perform trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed, and any data generated.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained, if necessary, to provide clarification.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF, must be given a written and dated approval or favorable opinion by an IRB or EC as appropriate. The Investigator must obtain and document approval before he or she can enroll any participant into the study. The IRB or EC must supply to the sponsor a list of the IRB/EC membership and a statement to confirm that the IRB/EC is organized and operates according to GCP and applicable laws and regulations.

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

The principal investigator is also responsible for providing the IRB or EC with reports of any reportable serious adverse drug reactions from any other study conducted with the IP. Sage Therapeutics will provide this information to the principal investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or EC according to local regulations and guidelines. In addition, the principal investigator must inform the IRB/EC and sponsor of any changes significantly affecting the conduct of the trial and/or increasing the risk to participants (eg, violations to the protocol or urgent safety measures taken for participant safety).

16.2. 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 are consistent with ICH and GCP guidelines, as well as all applicable regional or national regulatory requirements.

16.3. Written Informed Consent

Prior to enrolling a trial participant, the investigator(s) will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and allowed time to consider the information provided.

When the participant decides to participate in the trial, the participant (or the participant's, parent or legally authorized representative) must provide signed and dated informed consent. The written consent must be obtained before conducting any study procedures. The investigator must document the consent process in the participant's source records. The investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant or to the participant's parent or legally authorized representative.

Throughout the trial participants should be informed of any changes made to the study and as new safety and or risk information becomes known. The provision of this information will be documented in the participant's source records, and when applicable, an updated ICF will be provided.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Sage Therapeutics or its representative(s) will be allowed to conduct site visits at the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the facility, drug storage area, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

Inspection of the study by a regulatory authority may occur at any time. The investigator must agree to the inspection of study-related records and source documents by the regulatory authority representative(s).

17.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for the period outlined in the site contract, or for a period of 2 years after the last marketing application approval, and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Sage is responsible to inform the Investigator/institution as to when study documents no longer need to be retained.

18. PUBLICATION POLICY

All information concerning SAGE-324 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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A PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY EVALUATING THE EFFICACY, SAFETY, AND TOLERABILITY OF SAGE-324 IN THE TREATMENT OF INDIVIDUALS WITH ESSENTIAL TREMOR

324-ETD-201

Investigational Product	SAGE-324 Oral Tablet
Clinical Phase	Phase 2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted], MD
Sponsor Medical Monitor	[redacted], MD, PhD
Date of Original Protocol	23 October 2019
Date of Amendment 1	20 December 2019
Date of Amendment 2	24 February 2020

SPONSOR APPROVAL

Protocol Number:	324-ETD-201
Study Title:	A Phase 2, Double-Blind, Placebo-Controlled, Randomized Study Evaluating the Efficacy, Safety, and Tolerability of SAGE-324 in the Treatment of Individuals with Essential Tremor
Protocol Version and Date:	Version 3, 24 February 2020

[redacted], MS, RAC — Date

[redacted] — Date

[redacted], DVM — Date

[redacted] — Date

[redacted], PhD — Date

[redacted], PhD — Date

[redacted], MS — Date

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-324. I have read the 324-ETD-201 protocol 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 (DD/MMM/YYYY)

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Sage Study Physician	[redacted], MD	Phone [redacted]
Sage Medical Monitor and 24-hour Emergency Contact	[redacted], MD, PhD	Mobile: [redacted]1 Office phone: [redacted] E-mail: [redacted]
SAE Reporting Information	IQVIA Lifecycle Safety	4820 Emperor Boulevard Durham, NC 27703 E-mail: Sage.Safety@iqvia.com Fax: +1-855-638-1674 SAE Hotline: +1-855-564-2229
Product Complaints	Sage Therapeutics, Inc.	E-mail: productcomplaints@sagerx.com Phone: +1-833-554-7243

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics, Inc. (hereafter referred to as Sage Therapeutics, or Sage)

Name of Investigational Product:
SAGE-324 Oral Tablet

Name of Active Ingredient:
SAGE-324

Title of Study:
A Phase 2, Double-blind, Placebo-controlled, Randomized Study Evaluating the Efficacy, Safety, and Tolerability of SAGE-324 in the Treatment of Individuals with Essential Tremor

Number of Sites and Study Location: This study will take place at approximately 30 sites in the United States.

Phase of Development: Phase 2

Planned Duration for each Study Participant:
The duration of participation (from Screening through the final follow-up visit) for each participant is estimated to be up to 71 days.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the effect of SAGE-324 compared to placebo on upper limb tremor reduction in individuals with essential tremor (ET) after 28 days of treatment	Change from baseline compared to placebo in The Essential Tremor Rating Assessment (TETRAS) performance subscale part 4 upper limb tremor score on Day 29
Secondary	
To assess the effect of SAGE-324 compared to placebo on overall upper limb tremor reduction	• Change from baseline compared to placebo in TETRAS performance subscale part 4 upper limb tremor score at all other timepoints • Change from baseline compared to placebo in Kinesia ONE accelerometer scores
To assess the effect of SAGE-324 compared to placebo on activities of daily living (ADLs)	• Change from baseline compared to placebo in TETRAS Scale ADL score
To assess the effect of SAGE-324 compared to placebo on overall tremor	• Change from baseline compared to placebo in TETRAS total performance score
To evaluate the safety and tolerability of SAGE-324	• Incidence of treatment-emergent adverse events (TEAEs)

[redacted]

Study Description:

This is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of SAGE-324 in individuals with ET. Participants, site staff, and sponsor personnel will be masked to treatment allocation.

This study includes a Screening Period of up to 28 days, a 29-day treatment period (28 days of dosing), and a 14-day follow up period. After providing informed consent, participants will undergo screening assessments as outlined in Table 2 to determine eligibility.

Screening Period: The Screening Period begins with the signing of the informed consent form (ICF). Eligible participants will visit the study center on Day 1 and complete additional eligibility and baseline assessments, as specified in the Schedule of Assessments (Table 2). Following completion of screening

and Day 1 eligibility checks, participants will be randomized to 1 of 2 treatment groups (SAGE-324 60 mg daily, or placebo) in a 1:1 ratio. **Double-Blind Treatment Period:** Starting on Day 1, participants will receive a single dose of investigational product (IP) once daily for 28 days on an outpatient basis, to be taken in the morning with food that comprises a minimum of 400 calories. Doses occurring on scheduled clinic visits will be administered in the clinic, and doses occurring on all other days will be self-administered by the participant at home. During the Treatment Period, participants will return to the study center approximately once per week for efficacy and safety assessments as specified in Table 2. Participants will be trained on the use of software applications and devices necessary to complete questionnaires or other assessments. During the study, a phone call will be conducted once per week, preferably midway between clinic visits, to review current status of participant. **Follow-Up Period:** Follow-up visits will be conducted on an outpatient basis. Participants will continue to complete questionnaires as indicated in Table 2 and will receive a phone call approximately 7 days after the last dose of IP (ie, Day 35) for safety monitoring. Participants will return to the study center for an end of study visit approximately 14 days following the last dose of IP (ie, Day 42).
Number of Participants (planned): Approximately 60 participants, with approximately 30 per arm.

Eligibility Criteria:

Inclusion Criteria:

1. Participant has signed an ICF before any study-specific procedures or washout of drugs is performed.
2. Participant is ambulatory and is 18 to 80 years of age, inclusive, at the time informed consent is obtained.
3. Participant has a diagnosis of ET, as defined by all of the following criteria:
    a. Isolated tremor syndrome consisting of bilateral upper limb action tremor
    b. At least 3 years duration
    c. With or without tremor in other locations (eg, head, voice, or lower limbs)
    d. Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism, isolated focal tremors (eg, voice, head), task- and position-specific tremors, sudden tremor onset or evidence of stepwise deterioration of tremor
4. Participant scores at least 1.5 for each of the six items that comprise the combined total upper limb TETRAS (total performance subscale part 4) with the total score for the dominant upper limb (the sum of the 3 items for either the right or left upper limb, whichever is dominant) being at least 5.5, at both Screening and predose on Day 1.
5. Participant is willing to discontinue medications taken for the treatment of ET within 14 days or 5 half-lives (whichever is longer) prior to receiving IP. Medications taken for the treatment of ET that were discontinued prior to receiving IP may be resumed following Day 29.
6. Participant is willing to discontinue the use of alcohol and products that contain nicotine within at least 1 week prior to Day 1 and through Day 29 of the study.
7. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does include abstinence).
8. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 13 weeks after receiving study drug, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
9. Male participant is willing to abstain from sperm donation for the duration of the study and for 13 weeks after receiving study drug.
10. Participant has no clinically significant findings, as determined by the investigator, on Screening and predose Day 1 physical examination including mental state examination (MSE) and neurologic examination, 12-lead ECG, or screening clinical laboratory tests.

Exclusion Criteria:

1. Participant has presence of known causes of enhanced physiological tremor.

2. Participant has had recent exposure (14 days prior to Day 1) to tremorgenic drugs or presence of alcohol withdrawal state.
3. Participant has had direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor.
4. Participant has had a previous procedure for the treatment of ET, deep brain stimulation, brain lesioning, or magnetic resonance (MR) guided procedure, eg, MR-guided focused ultrasound.
5. Participant has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.)
6. Participant has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic (hypothyroidism with stable thyroid replacement is acceptable), or oncological disease.
7. Participant has history of substance abuse prior to Screening, has a positive screen for drugs of abuse at Screening or predose on Day 1, or has a positive screen for alcohol predose on Day 1.
8. Participant has a known allergy to SAGE-324 or any excipient.
9. Participant has had exposure to another investigational drug or device within 30 days or 5 half-lives (if known) of the investigational drug, whichever is longer, prior to the Day 1 visit.
10. Participant has history of suicidal behavior within 2 years or answers "YES" to questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk of suicide in the opinion of the investigator
11. Participant has donated one or more units (1 unit = 450 mL) of blood or experienced acute loss of an equivalent amount of blood within 60 days prior to Day 1.
12. Participant has any condition or comorbidity that in the opinion of the investigator would limit or interfere with the participant's ability to complete or partake in the study.
13. Participant is unwilling or unable to comply with study procedures and required training.
14. Participant has used any known moderate or strong cytochrome P450 3A4 inhibitors and/or inducers within 14 days or 5 half-lives (whichever is longer) prior to Day 1 or consumed grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St. John's Wort or products containing these within 30 days prior to Day 1. Use of mild cytochrome inhibitors and/or inducers may be permitted.
15. Participant has concurrent or recent exposure (14 days or five half-lives, whichever is longer, prior to the Day 1 visit) to sedative/hypnotic drugs, stimulants, highly caffeinated beverages or dietary supplements containing high doses of caffeine, or recent increase above regular daily consumption of caffeine.
16. Participant plans to undergo elective surgery or relocate during participation in the study.
17. Participant is investigative site personnel or a member of their immediate families (spouse, parent, child or sibling whether biological or legally adopted).

18. Participant currently uses or has used within 14 days or 5 half-lives (whichever is longer) prior to Day 1, any prescription or over-the-counter medication that is a substrate of the OATP1B1 transporter.
19. Female participant has a positive pregnancy test or confirmed pregnancy.

Investigational Product Dosage and Mode of Administration:

SAGE-324 (60 mg) or matched placebo oral tablets will be administered in the clinic or self-administered once daily, in the morning with food that comprises a minimum of 400 calories.

Duration of Treatment:

Each participant will receive a single dose of SAGE-324 oral tablets or matching placebo administered once daily for 28 days.

Statistical Methods:

A separate statistical analysis plan (SAP) will provide a detailed description of the data analyses to be performed in the study. The SAP will be finalized and approved prior to database lock.

General Considerations

For the purpose of all efficacy and safety analyses where applicable, baseline is defined as the last measurement prior to the start of IP administration.

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

Analysis Sets

The Randomized Set is defined as all participants who are randomized.

The Safety Set will include all participants who were administered IP.

The Full Analysis Set will include all randomized participants who received any amount of IP and have a baseline and at least one postbaseline TETRAS performance subscale part 4 upper limb tremor score.

[redacted]

The Per Protocol Set will include all participants in the Full Analysis Set without any major protocol deviations that could affect efficacy. The review of major protocol deviations will be completed, and the decision on whether the deviation affects efficacy will be documented before database unblinding.

Determination of Sample Size

The sample size of this study is based on the assumption of a 3-point difference in the change from baseline TETRAS performance subscale part 4 upper limb tremor scores between SAGE-324 and placebo with a standard deviation of 3.5 points. Under these assumptions, a sample size of 25 evaluable participants per group would provide 85% power for detecting a placebo-adjusted treatment difference of 3 points in TETRAS performance subscale part 4 upper limb tremor score, assuming a 2-sided test at an alpha level of 0.05. By including 2 treatment groups and using a 1:1 randomization, a total of 50 evaluable participants are required. Assuming a nonevaluability rate of 15%, approximately 60 participants will be randomized. Additional participants may be enrolled if the drop-out rate is higher than 15%.

Analysis of Primary Efficacy Endpoint

The estimand for the primary efficacy analysis is the treatment difference between SAGE-324 and placebo in mean change from baseline in clinic-based TETRAS performance subscale part 4 upper limb tremor score at Day 29 based on the Full Analysis Set. This will be analyzed using a mixed-effects

model for repeated measures (MMRM); the model will include treatment, baseline TETRAS performance subscale part 4 upper limb tremor score, assessment timepoint, and timepoint-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline clinic visits will be included in the model. The main comparison will be between SAGE-324 and placebo at the 29-day timepoint. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz compound symmetry or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not unstructured, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

Analysis of Secondary Efficacy Endpoints

Similar to those methods described above for the primary endpoint, an MMRM will be used to analyze of the change from baseline in TETRAS total performance scores, Kinesia ONE accelerometer scores and TETRAS ADL scores. Individual items of the TETRAS subscales will be summarized.

Safety Analysis

Safety and tolerability of study drug will be evaluated by incidence of TEAEs/serious adverse events,

[redacted]

Interim Analysis

The sponsor may conduct an interim analysis. Detailed descriptions of planned data analyses will be provided in a separate interim statistical analysis plan (SAP), if applicable.

Table 2: Schedule of Assessments

Assessment	Screening	Treatment Period									Follow-up Period	
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15(±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**35 (±1) Safety Phone Call**	**42 (±1) EOS/ETV**
Informed Consent	X											
Inclusion/Exclusion	X	X										
Demographics	X											
Medical History	X											
Pregnancy Test[l]	X (serum; all women)	X (urine; WOCBP only)				X (urine; WOCBP only)				X (urine; WOCBP only)		X (urine; WOCBP only)
FSH (postmenopausal women only)	X											
Randomization[a]		X										
Alcohol/cotinine screens		X		X		X		X		X		
Drug screen	X	X										
Physical examination[b]	X	X		X		X		X		X		X
Neurological examination including MSE[b]	X	X		X		X		X		X		X
Body height	X											
Body weight	X											
Vital signs[c]	X	X		X		X		X		X		X
12-Lead ECG[d]	X	X		X		X		X		X		X
Chemistry/hematology/ coagulation/urinalysis	X	X		X		X		X		X		X
[redacted]												

Assessment	Screening	Treatment Period									Follow-up Period	
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15(±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**35 (±1) Safety Phone Call**	**42 (±1) EOS/ETV**
[redacted]												
Kinesia[f]	X	X		X		X		X		X		X
TETRAS[g]	X	X		X		X		X		X		X
[redacted]												

Assessment	Screening	Treatment Period									Follow-up Period	
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15(±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**35 (±1) Safety Phone Call**	**42 (±1) EOS/ETV**
Patient Perception of Response Burden										X		X
[redacted]												
Participant training[h]	X	X										
Dispense study drug		X		X		X		X				
IP administration		Administered once daily for 28 days							Not applicable			
AEs/SAEs	X											
Prior and concomitant medication and history[i]	X											

Abbreviations: ADL = activities of daily living; AE = adverse event; [redacted]; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; [redacted]; ETV = early termination visit; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; ICF = informed consent form; min = minutes; IP = investigational product; MSE = mental state examination; [redacted]; SAE = serious adverse event; TETRAS = The Essential Tremor Rating Assessment Scale; WOCBP = women of childbearing potential

Notes:

- The suggested order of assessments during clinic visits is: vital signs, TETRAS, Kinesia, ECG, blood sample collection for [redacted] and clinical laboratory assessments, and questionnaires.
- All assessments will be performed predose unless specified in a footnote.

[a] Randomization will occur on Day 1 after meeting all eligibility criteria.

[b] Complete physical examinations (including MSE and neurologic examination as parts of physical examination) should be performed as specified and as clinically necessary (see Section 12.1.3).

[c] Predose on Day 1, supine and standing blood pressure and heart rate will be collected in triplicate at least 15 minutes apart, measured after the participant has been in the supine position for at least 5 minutes and then repeated 1 minute and 3 minutes after standing. Respiratory rate and temperature are collected once predose on Day 1. Vital signs will be collected once predose at all other visits. All postdose vital signs will be collected once at approximately 3 hours (±60 min) after dosing.

[d] ECGs will be collected and read centrally. ECGs will be performed predose and approximately 3 hours (±60 min) postdose. All ECGs must be performed after the participant has been in a supine position for at least 5 minutes.

[redacted]

[f] Kinesia ONE will be assessed simultaneously to TETRAS Performance subscale part 4 upper limb tremor.

[g] The TETRAS Performance and TETRAS ADL subscales will be assessed at Screening and predose at each clinic visit. The TETRAS Performance subscale part 4 upper limb tremor will be assessed simultaneously to Kinesia ONE. In addition, on Day 15, the TETRAS Performance subscale will be assessed at 5 and 8 hours (±30 min) postdose. A videographer will record each TETRAS administration.

[h] Participants will be trained by study personnel on the use of software applications, Investigational Product Diary, and devices necessary for the conduct of the study.

[i] Prior medications will be recorded during Screening and will include all medications and supplements taken within the 30 days prior to signing the ICF through the first dose of IP, as well as a complete history of all treatments for ET since the year of diagnosis. Concomitant medications will be recorded thereafter throughout the duration of the study.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ADL	activities of daily living
AUC_{inf}	area under the curve from 0 to infinity
$AUC_{0\text{-}tau}$	area under the concentration-time curve from 0 to end of the dosing period
BMI	body mass index
[redacted]	[redacted]
C_{max}	maximum observed concentration
CRO	contract research organization
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End-of-Study
[redacted]	[redacted]
[redacted]	[redacted]
ET	essential tremor
[redacted]	[redacted]
ETV	early termination visit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
PD	pharmacodynamic
[redacted]	[redacted]
PI	principal investigator
PK	pharmacokinetic

Abbreviation	Definition
[redacted]	
PV	Pharmacovigilance
QTcF	QT corrected according to Fridericia's formula
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
t_{max}	time of occurrence of C_{max}
WHO	World Health Organization

5. INTRODUCTION

SAGE-324 is a positive allosteric modulator (PAM) of A-type γ-aminobutyric acid-gated chloride channel ($GABA_A$) receptors, the major class of inhibitory neurotransmitter receptors in the brain. In addition to being developed as an adjunctive therapy in epilepsy and other seizure disorders under IND 139201, SAGE-324 is also being developed for the treatment of Essential Tremor (ET).

Essential tremor is a permanently debilitating, neurologically determined, common movement disorder characterized by involuntary rhythmic oscillation of a body part due to intermittent muscle contractions typically occurring when not at rest, thus interfering with fine motor skills associated with daily activities (Olanow 2008, Deuschl 2011, Hopfner 2016, NIH 2019). Although the pathophysiology and etiology of ET is not fully understood, it is postulated that approximately 50% of ET patients feature an autosomal dominant pattern of familial inheritance and that non-inherited cases may have toxin-based or other causality (Olanow 2008, Hopfner 2016). ET is the most common movement disorder in the US, with prevalence estimated to be approximately 2.2% of the population, representing a substantial societal medical burden with over an estimated 7 million ET patients in the US alone (Louis 2014).

In general, active tasks of daily life are adversely impacted by ET, including but not limited to speech, handwriting, household tasks, and occupational demands, contributing negatively to psychosocial well-being, general anxiety, and overall quality of life (Koller, 1989). Although benign in term of its effect on life expectancy, ET is a progressive neurodegenerative condition whose symptoms are typically disabling, often forcing patients to change jobs or seek early retirement (Zappia, 2013). In some cases, serious disability may ensue.

The pharmacological profile of SAGE-324 is theorized to induce therapeutic effect in the treatment of ET. Based on preclinical studies of SAGE-324, which features a different mechanism of action than that of propranolol, the pharmacokinetic (PK)/ pharmacodynamic (PD) profile suggests SAGE-324 may safely ameliorate symptoms in patients suffering from ET, regardless of propranolol use.

There are currently ongoing Phase 1 clinical studies of SAGE-324 in healthy adults and in adults with ET. These studies, in addition to preclinical studies of SAGE-324, are detailed in the investigator's brochure.

With a $GABA_A$ receptor-based mechanism of action featuring positive allosteric modulation capability, SAGE-324 represents a novel approach to the treatment of ET, which may help address the unmet medical need of the ET population, warranting further study of SAGE-324 as a potential treatment for this common movement disorder.

Henceforth, this double-blind, placebo-controlled efficacy and safety study of SAGE-324 will be conducted in adults and is designed to assess the effect of SAGE-324 on a variety of outcome measures specific to ET disease characteristics and associated quality of life domains.

5.1. Dose Justification

The dose of SAGE-324 planned for this study is 60 mg given as oral tablets, to be administered once daily in the morning with food. The dose was selected based on preliminary data from 3 active studies of SAGE-324, which included: unblinded data from completed cohorts in

324-CLP-101 Part A (oral solution SAGE-324 doses of 3 mg, 10 mg, 30 mg, 45 mg, 60 mg); Part C (oral solution SAGE-324 doses of 30 mg); Part D (oral suspension SAGE-324 doses of 30 mg) in healthy subjects; and preliminary data from open-label Part E (oral suspension SAGE-324 doses of 45 mg and 60 mg) in participants with ET; additional preliminary data from 324-CLP-102 cohorts 1 through 6 (cohorts 1 to 5 unblinded, cohort 6 blinded), which evaluated oral suspension doses ranging from 5 mg to 60 mg; and preliminary unblinded data from 324-CLP-104, which compared the relative bioavailability of the oral tablet (30 mg) vs oral suspension (30 mg) formulations of SAGE-324 and separately the effect of food on the PK of the SAGE-324 oral tablet. In 324-CLP-101 and 324-CLP-102 studies, doses were administered in a fasted state. The preliminary data from all of these active studies collectively informed the route of administration (oral) and dose strength of 60 mg as oral tablets planned for further evaluation in this study.

SAGE-324 was generally well-tolerated in participants with ET and in healthy volunteers, as was shown in the preliminary data of 324-CLP-101 Part E at single administration doses of 45 mg and 60 mg, and in 324-CLP-102 through once-daily administered doses of up to 60 mg for 14 days. In addition, tremor reduction was observed at both doses on TETRAS and Kinesia accelerometry, with greater improvement seen at 60 mg compared to 45 mg.

In the clinically complete study 324-CLP-104, preliminary data showed that SAGE-324 oral tablets, when coadministered with a meal, resulted in exposures approximately equivalent to that of SAGE-324 oral suspension under fasted conditions. Therefore, the SAGE-324 oral tablets are recommended to be administered with food.

5.2. Benefit/Risk Assessment

Based on the mechanism of action of SAGE-324 and the results of completed nonclinical studies and preliminary data of currently ongoing clinical studies of SAGE-324, it is theorized that participants may have symptomatic amelioration, ie, tremor reduction and possibly improved quality of life from potentially stabilizing disease characteristics associated with ET.

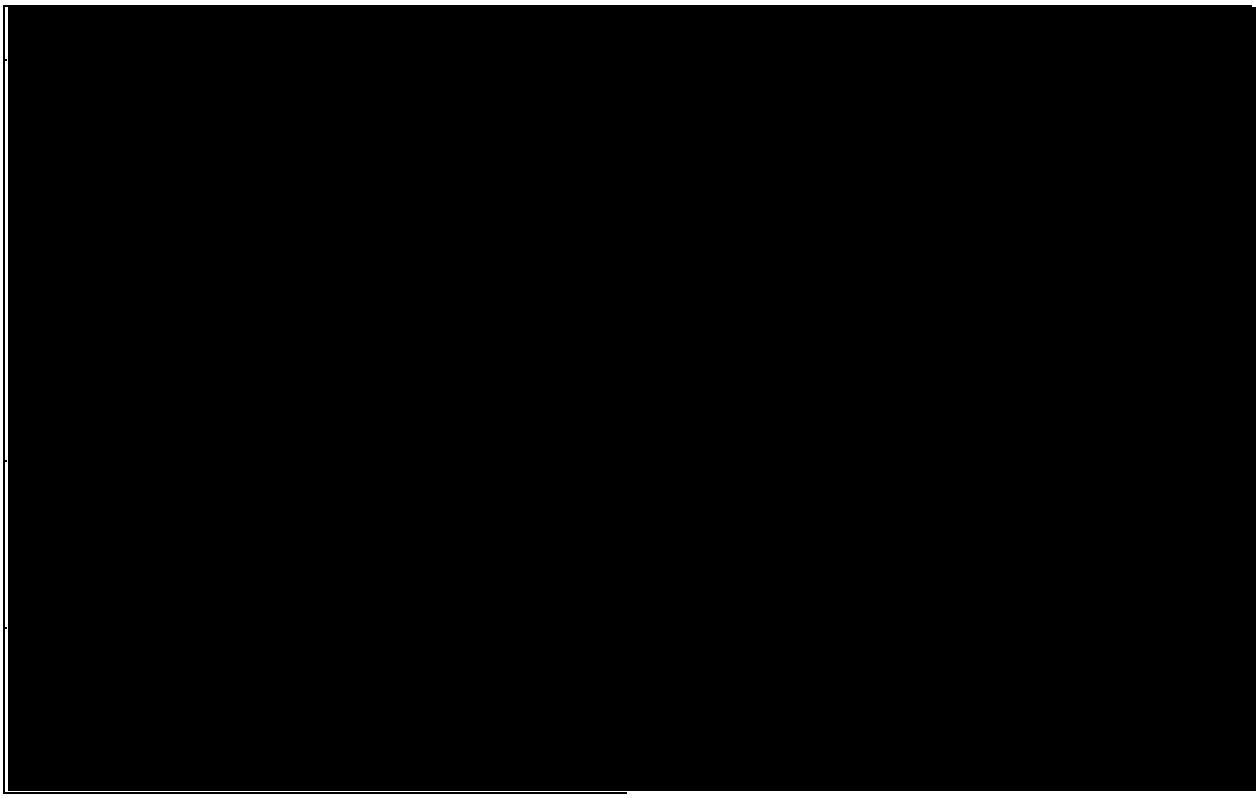
Potential risks anticipated in this study are based on available data from toxicology studies of SAGE-324 in addition to preliminary data from 3 ongoing, currently active Phase 1 clinical studies of SAGE-324.

Available preliminary clinical data are summarized in the SAGE-324 Investigator's Brochure. There have been no deaths or SAEs related to IP, and based on the preliminary clinical data available, there have been no confirmed clinically significant trends in clinical laboratory evaluations, vital signs, or physical examinations.

Based on available preliminary clinical data from SAGE-324 active clinical studies, AEs of somnolence and feeling of relaxation are considered adverse drug reactions. In addition to scheduled clinic visits, the current status of study participants will be reviewed via weekly phone calls, in between clinic visits.

6. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the effect of SAGE-324 compared to placebo on upper limb tremor reduction in individuals with essential tremor (ET) after 28 days of treatment	Change from baseline compared to placebo in The Essential Tremor Rating Assessment (TETRAS) performance subscale part 4 upper limb tremor score on Day 29
Secondary	
To assess the effect of SAGE-324 compared to placebo on overall upper limb tremor reduction	• Change from baseline compared to placebo in TETRAS performance subscale part 4 upper limb tremor score at all other timepoints • Change from baseline compared to placebo in Kinesia ONE accelerometer scores
To assess the effect of SAGE-324 compared to placebo on activities of daily living (ADLs)	• Change from baseline compared to placebo in TETRAS Scale ADL score
To assess the effect of SAGE-324 compared to placebo on overall tremor	• Change from baseline compared to placebo in TETRAS total performance score
To evaluate the safety and tolerability of SAGE-324	• Incidence of treatment-emergent adverse events (TEAEs)
[redacted]	



7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of SAGE-324 in individuals with ET. Participants, site staff, and sponsor personnel will be masked to treatment allocation (see Section 9.5).

This study includes a Screening Period of up to 28 days, a 29-day treatment period consisting of 28 days of dosing with the end of treatment visit intended to be on Day 29 at trough, and a 14-day follow-up period relative to final dose (Figure 1). After providing informed consent, participants will undergo screening assessments as outlined in Table 2 to determine eligibility.

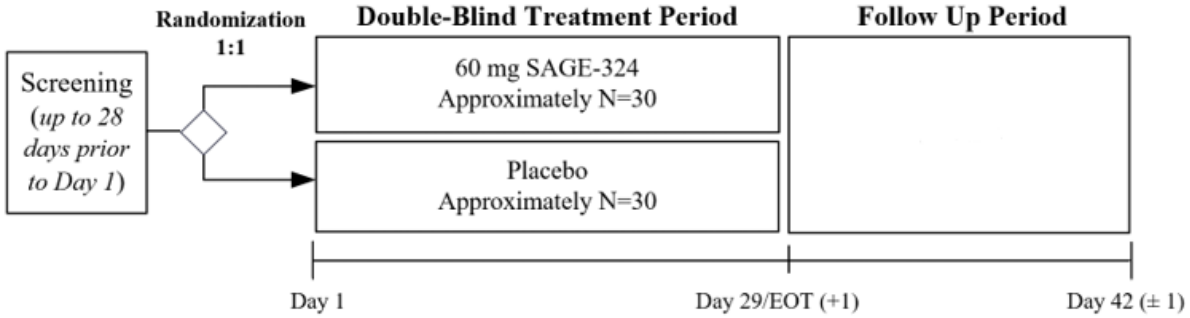
The Screening Period begins with the signing of the informed consent form (ICF). Eligible participants will visit the study center on Day 1 and complete additional eligibility assessments of safety and efficacy, as specified in the Schedule of Assessments (Table 2). Following completion of screening and Day 1 eligibility checks, participants will be randomized to 1 of 2 treatment groups (SAGE-324 60 mg daily, or placebo) in a 1:1 ratio.

During the double-blind Treatment Period, starting on Day 1, participants will receive a single dose of investigational product (IP) once daily in the morning with food for 28 days on an outpatient basis. Doses occurring on scheduled clinic visits will be administered in the clinic, and doses occurring on all other days will be self-administered by the participant at home as specified in Table 2. During the Treatment Period, participants will return to the study center approximately once per week for efficacy and safety assessments as specified in Table 2. In addition, a phone call will be conducted once per week, preferably mid-way between clinic visits, to review current status of the participant.

In addition to Kinesia ONE-specific training, clinical study center staff and study participants will be trained on the use of software applications and devices necessary to complete questionnaires or other assessments as required. During in-clinic visits, clinical study center staff will be available to assist participants as needed, to ensure they can access and use the software applications and devices correctly according to the training.

During the follow-up period, visits will be conducted on an outpatient basis. In addition to the phone calls to review current status, participants will receive a phone call approximately 7 days after the last dose of IP (ie, Day 35) for safety monitoring. Participants will return to the study center for an end of study visit approximately 14 days following the last dose of IP (ie, Day 42).

Figure 1: Study Design



Abbreviation: EOT = end of treatment

7.2. Number of Participants

Approximately 60 participants are planned, with approximately 30 participants enrolled per arm, to produce 25 evaluable participants per arm for primary efficacy analysis. Additional participants may be randomized if the drop-out rate is higher than anticipated (ie, >15%).

7.3. Treatment Assignment

Participants will be assigned to IP (active or placebo) in accordance with the randomization schedule on Day 1. Additional details on randomization and blinding are provided in Section 9.5.

7.4. Dose Adjustment Criteria

If participants report adverse events that are considered by the investigator to be related to the IP and not tolerable, the investigator may reduce the dose of IP from 60 mg in 15 mg decrements (ie, 60, to 45, to 30 mg), as medically appropriate. The dose may not be reduced below 30 mg: if intolerable adverse events persist at the 30 mg dose, the IP should be permanently stopped. The reduced dose of IP will continue to be administered once daily at the same schedule as specified in the Schedule of Assessments (Table 2). The dose of IP may not be increased for the remainder of the study.

Otherwise, IP doses will not be further adjusted for this study except as clinically necessary, eg, interrupting dose due to an AE or serious adverse event (SAE) considered related to IP.

7.5. Criteria for Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to participants, 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 IRB, where required, and initiate withdrawal procedures for participating participants.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

Participants must meet all of the following criteria to qualify for participation in this study:

1. Participant has signed an ICF before any study-specific procedures or washout of drugs is performed.
2. Participant is ambulatory and is 18 to 80 years of age, inclusive, at the time informed consent is obtained.
3. Participant has a diagnosis of ET, as defined by all of the following criteria:
    a. Isolated tremor syndrome consisting of bilateral upper limb action tremor
    b. At least 3 years duration
    c. With or without tremor in other locations (eg, head, voice, or lower limbs)
    d. Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism, isolated focal tremors (eg, voice, head), task- and position-specific tremors, sudden tremor onset or evidence of stepwise deterioration of tremor
4. Participant scores at least 1.5 for each of the six items that comprise the combined total upper limb TETRAS (total performance subscale part 4) with the total score for the dominant upper limb (the sum of the three items for either the right or left upper limb, whichever is dominant) being at least 5.5, at both Screening and predose on Day 1.
5. Participant is willing to discontinue medications taken for the treatment of ET within 14 days or 5 half-lives (whichever is longer) prior to receiving IP. Medications taken for the treatment of ET that were discontinued prior to receiving IP may be resumed following Day 29.
6. Participant is willing to discontinue the use of alcohol and products that contain nicotine within at least 1 week prior to Day 1 and through Day 29 of the study.
7. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does include abstinence).
8. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 13 weeks after receiving study drug, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
9. Male participant is willing to abstain from sperm donation for the duration of the study and for 13 weeks after receiving study drug.
10. Participant has no clinically significant findings, as determined by the investigator, on Screening and predose Day 1 physical examination including mental state examination (MSE) and neurologic examination, 12-lead ECG, or screening clinical laboratory tests.

8.2. Participant Exclusion Criteria

Participants who meet any of the following criteria are disqualified from participation in this study:

1. Participant has presence of known causes of enhanced physiological tremor.
2. Participant has had recent exposure (14 days prior to Day 1) to tremorgenic drugs or presence of alcohol withdrawal state.
3. Participant has had direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor.
4. Participant has had a previous procedure for the treatment of ET, deep brain stimulation, brain lesioning, or magnetic resonance (MR) guided procedure, eg, MR-guided focused ultrasound.
5. Participant has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.)
6. Participant has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic (hypothyroidism with stable thyroid replacement is acceptable), or oncological disease.
7. Participant has history of substance abuse prior to Screening or has a positive screen for drugs of abuse at Screening or predose on Day 1 or has a positive screen for alcohol predose on Day 1.
8. Participant has a known allergy to SAGE-324 or any excipient.
9. Participant has had exposure to another investigational drug or device within 30 days or 5 half-lives (if known) of the investigational drug, whichever is longer, prior to the Day 1 visit.
10. Participant has history or suicidal behavior within 2 years or answers “YES” to questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk or suicide in the opinion of the investigator
11. Participant has donated one or more units (1 unit = 450 mL) of blood or experienced acute loss of an equivalent amount of blood within 60 days prior to Day 1.
12. Participant has any condition or comorbidity that in the opinion of the investigator would limit or interfere with the participant’s ability to complete or partake in the study.
13. Participant is unwilling or unable to comply with study procedures and required training.
14. Participant has used any known moderate or strong cytochrome P450 3A4 inhibitors and/or inducers within 14 days or 5 half-lives (whichever is longer) prior to Day 1 or consumed grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St. John’s Wort or products containing these within 30 days prior to Day 1. Use of mild cytochrome inhibitors and/or inducers may be permitted.
15. Participant has concurrent or recent exposure (14 days or 5 half-lives, whichever is longer, prior to the Day 1 visit) to sedative/hypnotic drugs, stimulants, highly caffeinated

beverages or dietary supplements containing high doses of caffeine, or recent increase above regular daily consumption of caffeine.

16. Participant plans to undergo elective surgery or relocate during participation in the study.
17. Participant is investigative site personnel or a member of their immediate families (spouse, parent, child or sibling whether biological or legally adopted).
18. Participant currently uses or has used within 14 days or 5 half-lives (whichever is longer) prior to Day 1, any prescription or over-the-counter medication that is a substrate of the OATP1B1 transporter.
19. Female participant has a positive pregnancy test or confirmed pregnancy.

8.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned IP or entered in the study, ie, a participant who does not meet 1 or more of the eligibility criteria after providing consent and prior to randomization (Day 1). A minimal set of screen failure information will be collected, including demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

8.4. Investigational Product Discontinuation and Early Termination from the Study

8.4.1. Investigational Product Discontinuation

A participant may discontinue IP at any time at his/her own request for any reason. The investigator may discontinue a participant from IP for safety, behavioral, compliance, or administrative reasons. Participants who discontinue IP will be encouraged by the investigator to remain on study and complete the EOT visit, the safety phone call 7 days later, and then, after a further 7 days, the End of Study/Early Termination visit (EOS/ETV), as specified in the Schedule of Assessments (Table 2). If the participant withdraws consent to collect protected health information, the EOS/ETV will be conducted.

The reason for IP discontinuation must be documented in the participant's study record and recorded in the participant's electronic case report form (eCRF).

The investigator must notify the sponsor and/or the medical monitor when a participant stops IP for any reason.

Participants who discontinue IP due to an AE, regardless of investigator-determined causality, should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant.

8.4.2. Early Termination from the Study

A participant may withdraw from the study at any time at his/her own request for any reason. The investigator may discontinue a participant from the study for safety, behavioral, compliance, or administrative reasons.

The reason for early termination from the study must be documented in the participant's study record and recorded in the participant's electronic case report form (eCRF).

The investigator must notify the sponsor and/or the medical monitor when a participant stops participation in the study for any reason.

If a participant is persistently noncompliant, the investigator should discuss with the sponsor the potential discontinuation of the participant. Any reasons for unwillingness or inability to adhere to the protocol must be recorded in the participant's eCRF, including:

- missed visits;
- interruptions in the schedule of study drug administration;
- non-permitted medications

If the participant withdraws from the study after completing 28 days of dosing with IP, they will be encouraged to attend follow-up visits for safety assessments at Day 35 and Day 42, as specified in the Schedule of Assessments (Table 2). If the participant withdraws their consent to collect protected health information, the EOS/ETV visit will be conducted and the participant will be permanently discontinued from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor will retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

8.4.3. Loss to Follow-up

A participant will be deemed lost to follow-up after 3 attempts at contacting the participant have been unsuccessful.

8.4.4. Replacement of Participants

Participants will not be replaced.

9. TREATMENT OF PARTICIPANTS

9.1. Description of Investigational Product

SAGE-324 is an orally administered tablet provided in 5 mg or 15 mg (when available) dose strengths. Participants will receive IP (60 mg total dose of SAGE-324 tablets, or appearance-matched placebo tablets) according to the randomization schedule. Additional details regarding IP preparation, formulation, and storage are included in Section 10.

9.2. Prior Medications, Concomitant Medications, Restrictions, and Contraception Requirements

9.2.1. Prior and Concomitant Medications and/or Supplements

The start and end dates, route, dose/units, frequency, and indication for all medications and/or supplements taken within 30 days prior to signing the informed consent through the first dose of IP will be recorded.

All medications and/or supplements taken from the first dose of IP through the Day 42 (±1 days) visit (including start and end dates route, dose/units, frequency, and indication) will be recorded on the eCRF. Any concomitant medication determined necessary for the welfare of the participant may be given at the discretion of the investigator at any time during the study.

9.2.2. Prohibited Medications

Use or consumption of the following is prohibited for the timeframes specified:

- Treatment with an investigational drug or device during the 30 days or 5 half-lives (if known) of the investigational drug, whichever is longer, prior to Day 1 or during the study.
- Use of tremorgenic drugs within the 14 days or 5 half-lives (whichever is longer) of Day 1 or during the study.
- Use of agents known to affect SAGE-324 drug metabolism (any known cytochrome P450 3A4 inhibitors and/or inducers) within the 14 days or 5 half-lives (whichever is longer) of Day 1 and through Day 29 of the study period. Use of mild cytochrome P inhibitors and/or inducers may be permitted.
- Concomitant use of any prescription or over-the-counter medication that is a substrate of the OATP1B1 transporter for 14 days or 5 half-lives prior to Day 1 and during the 28-day dosing period.
- Concomitant use of sedative/hypnotic drugs for 14 days or 5 half-lives prior to Day 1 and during the 28-day dosing period.

9.2.3. Other Restrictions

- Use of any drugs of abuse during the study period is prohibited. Note: participants with a history of drug abuse prior to screening should not be enrolled in the study.

- Use of alcohol within 1 week prior to Day 1 and through Day 29 of the study period is prohibited. If the alcohol test is positive on Days 1, 8, 15, 22, or 29, the participant will not be administered further IP and will be withdrawn from the study; no further efficacy assessments such as TETRAS will be undertaken.
- Use of products that contain nicotine within 1 week prior to Day 1 and through Day 29 of the study period is prohibited. Positive cotinine testing on Days 1, 8, 15, 22, or 29 would be considered a major protocol deviation and the participant will be excluded from the Per Protocol Analysis Set.
- Consumption of grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St. John's Wort or products containing these within 30 days prior to Day 1 and through Day 29 of the study period is prohibited.
- Use of stimulants, highly caffeinated beverages or dietary supplements containing high doses of caffeine within 14 days prior to the Day 1 visit and through Day 29 of the study period is prohibited. Note: participants should not increase their regular daily consumption of caffeine during the study period.

9.2.4. Acceptable Forms of Contraception

Acceptable forms of highly effective contraception for participants of childbearing potential or for partners of male participants who are of childbearing potential include:

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal ligation or bilateral tubal occlusion (performed at least 3 months prior to Screening)
- Vasectomized partner (performed at least 3 months prior to Screening)
- Sexual abstinence (no sexual intercourse)

Acceptable forms of contraception for male participants include:

- Sexual abstinence (no sexual intercourse)
- History of vasectomy (performed at least 3 months prior to Screening)
- Condom with spermicide used together with highly effective female contraceptive methods if the female partner(s) is of childbearing potential (see above for list of acceptable female contraceptive methods)

9.3. Intervention after the End of the Study

There is no planned intervention following the end of the study.

9.4. Treatment Adherence

The first dose of IP will be received and administered by participants in the clinic. Participants will be dispensed a 7-day supply of IP to orally self-administer at home with instructions specifying to administer in the morning with food. Treatment adherence will be monitored by the site staff at each in-clinic visit by direct questioning and counting returned tablets and will be documented. Details on drug accountability are included in Section 10.6.

Patients will be asked to record the dates and times of their IP dose administrations at home in a diary. They will also record details around how well they complied with the study instructions for self-administering IP at home.

9.5. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Participants will be randomized in a 1:1 ratio to treatment groups (SAGE-324, 60 mg or placebo). Participants, site staff, and the sponsor will be blinded to treatment allocation. Randomization schedules will be generated by an independent statistician. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

9.5.1. Emergency Unblinding

During the study, the blind is to be broken only when the safety of a participant is at risk and the treatment plan is dependent on the study treatment received. Unless a participant is at immediate risk, the investigator should make diligent attempts to contact Sage prior to unblinding the study treatment administered to a participant. Requests from the investigator about the treatment administered to study participants should be discussed with the Sage Medical Monitor. If the unblinding occurs without Sage's knowledge, the investigator must notify Sage within 24 hours of breaking the blind. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

In all cases where the IP allocation for a participant is unblinded, pertinent information (including the reason for unblinding) must be documented in the participant's records and on the eCRF.

If a participant or any study personnel become unblinded to treatment, the participant will be excluded from the Per Protocol analysis set, as detailed further in the statistical analysis plan.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

Table 3: Investigational Product

	Investigational Product	
Product Name:	SAGE-324	Placebo
Dosage Form:	Tablet	Tablet
Tablet Strength	5 mg, 15 mg	0 mg, appearance-matched to 5 mg, and 15 mg, respectively
Route of Administration	Oral	Oral
Physical Description	Immediate release white to off-white, round, film-coated tablet containing 5 mg or 15 mg of SAGE-324 drug substance, and composed of lactose, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and fumed silica, featuring Opadry® II white as the coating agent.	White to off-white, round, film-coated tablet containing no drug substance, composed of lactose, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and fumed silica, featuring Opadry® II white as the coating agent.
Manufacturer	Sage Therapeutics, Inc.	

10.2. Investigational Product Packaging and Labeling

SAGE-324 Oral Tablets and Placebo Tablets will be packaged in blinded, high density polyethylene (HDPE) containers. The containers used for SAGE-324 and placebo will be identical in appearance. The package labeling conforms to FDA and GMP requirements.

10.3. Investigational Product Storage

Upon receipt of the IP, the investigator, or the responsible pharmacist or designee, will inspect the product and acknowledge receipt in accordance with the study-specific process.

The IP must be carefully stored at the temperature specified in the investigator's brochure, securely and separately from other drugs. The IP may not be used for any purpose other than the present study. Any unused IP must be returned per the sponsor's instructions or destroyed locally per the site's procedure(s). IP may not be destroyed until accountability and reconciliation procedures have been completed and monitored.

The investigator or designee will be responsible for ensuring appropriate storage, dispensing, inventory, and accountability of the IP. An accurate, timely record of the disposition of the IP must be maintained.

10.4. Investigational Product Preparation

The IP will be in tablet form and provided in blinded packaging. No preparation is required for the tablet, which is administered orally as described below.

10.5. Investigational Product Administration

The IP will be administered in the clinic or at home as specified in the Schedule of Assessments (Table 2). The IP will be provided as tablets, sufficient in number to achieve a dose of 60 mg. IP will be orally administered once daily in the morning, with food. Patients will be instructed to take the IP with food that comprises a minimum of 400 calories.

10.6. Investigational Product Accountability, Handling, and Disposal

Upon receipt of IP, the investigator(s), or the responsible pharmacist or designee, will inspect the IP and complete and follow the instructions regarding receipt and storage in the investigator's brochure and (where applicable) in the Pharmacy Manual. A copy of the shipping documentation will be kept in the study files.

The designated site staff will dispense the supplied participant-specific kits to participants at the planned dispensation visit intervals outlined in the Schedule of Assessments (Table 2).

An interactive response technology (IRT) will be used to capture participant-identifying information. The IRT will be used to randomize the eligible participant into the study and provides the kit number of the IP to be dispensed to that participant.

If dispensing errors or discrepancies are discovered by site staff or sponsor's designee, the sponsor must be notified immediately.

The IP provided is for use only as directed in this protocol. The investigator or designee must keep a record of all IP received, used and returned/discarded.

Sage Therapeutics will be permitted access to the study supplies at any time with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

The investigator, pharmacist, or qualified designee is responsible for drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

At the end of the study, any unused IP tablets will be returned to Sage Therapeutics for destruction or destroyed locally per the site's procedures; disposition of IP will be documented. IP may not be destroyed until accountability and reconciliation procedures have been completed and monitored.

10.7. Product Complaints

A product complaint is any written, electronic, or verbal expression of dissatisfaction regarding the identity, quality, reliability, safety, purity, potency, effectiveness or performance (applicable for approved marketed products) of a drug product after it is released for distribution.

In the course of conduct of the study, study personnel may become aware of a product complaint associated with the use of a Sage product. Personnel shall notify Sage within 24 hours by forwarding the product complaint information via the contact information listed in Table 1 and in

the Pharmacy Manual. Where possible, personnel should segregate and retain any product, materials, or packaging associated with the product complaint until further instruction is provided by Sage or its designated representative(s).

11. EFFICACY ASSESSMENTS AND CLINICAL PHARMACOLOGY ASSESSMENTS

11.1. Efficacy Assessments

11.1.1. The Essential Tremor Rating Assessment Scale

TETRAS is a validated, comprehensive clinical assessment of essential tremor (Elble 2013).

Three different components of TETRAS will be assessed in this study. The TETRAS ADL subscale, total performance score, and performance subscale part 4 upper limb tremor score will each be separately assessed at each clinic visit as specified in the Schedule of Assessments (Table 2).

The ADL subscale assesses how ET is impacting typical activities of daily living (ie, speech, eating, drinking, dressing, personal hygiene, writing, occupational impairment, social impact, and activities affected by upper limb tremor). It consists of 12 items that are each rated on a scale from 0 (normal activity) to 4 (severe abnormality). The overall ADL score range is 0 to 48.

The total performance score is based on overall rating of tremor amplitude in the voice, limbs, head, face, trunk, while performing pre-specified tasks, and also measures functional task capabilities, ie, handwriting, spirography, and holding a pen over a dot. Each of these items is rated on a scale from 0 (no tremor) to 4 (severe tremor). Collectively, the performance items generate an overall performance score from 0 to 64.

For the performance subscale part 4 upper limb tremor score, all 3 maneuvers in the upper limb assessments of part 4 (subscale items 4a, 4b, and 4c) will be completed for both arms, first for the left arm and then for the right. The part 4 subscale ordinally rates postural (limbs extended forward maneuver, and wing-beating [elbows flexed] maneuver), and kinetic (finger-nose-finger maneuver) tremor on a 0 to 4 severity scale in 0.5-point increments.

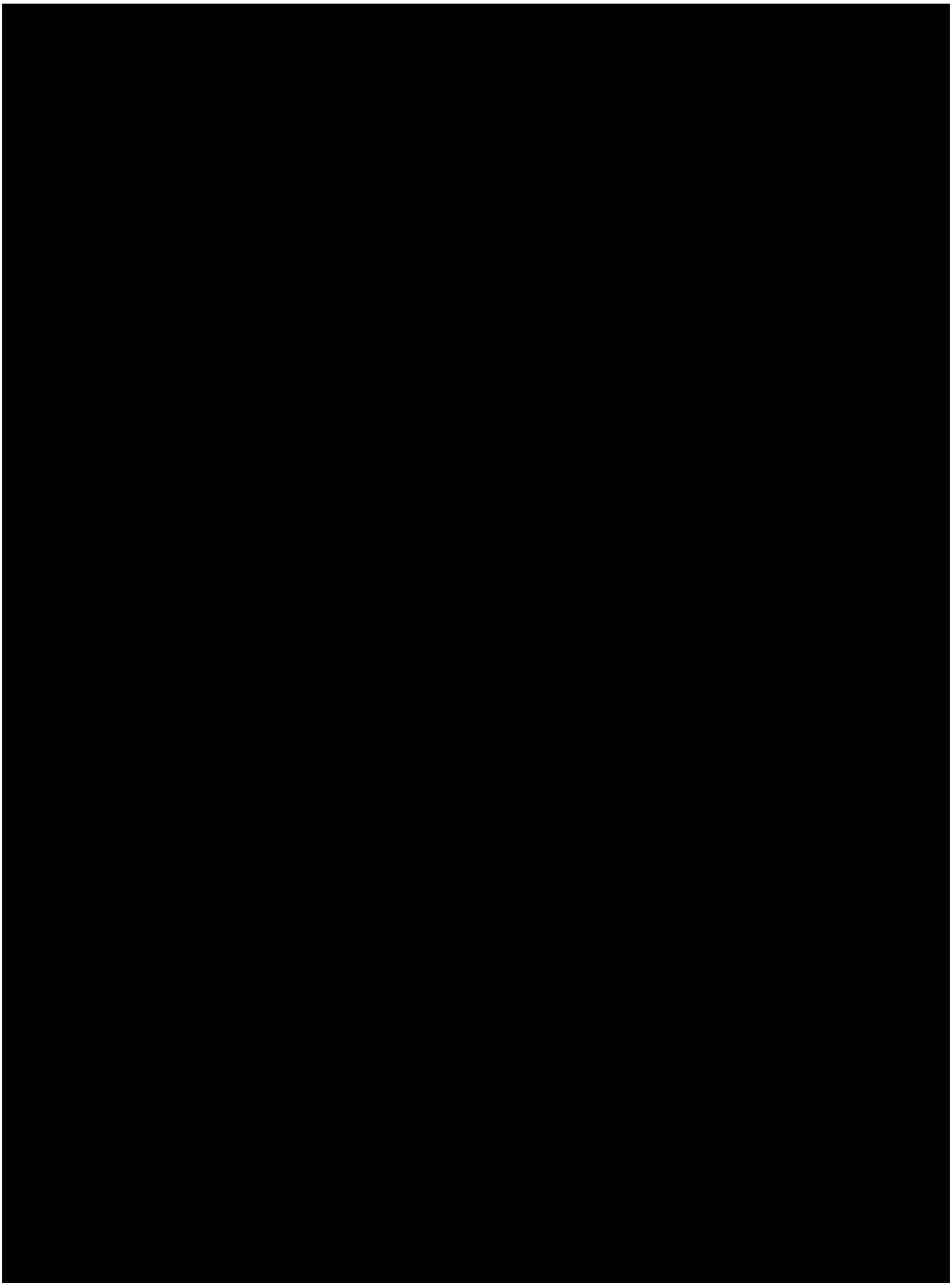
In this study, a videographer will videotape each TETRAS administration.

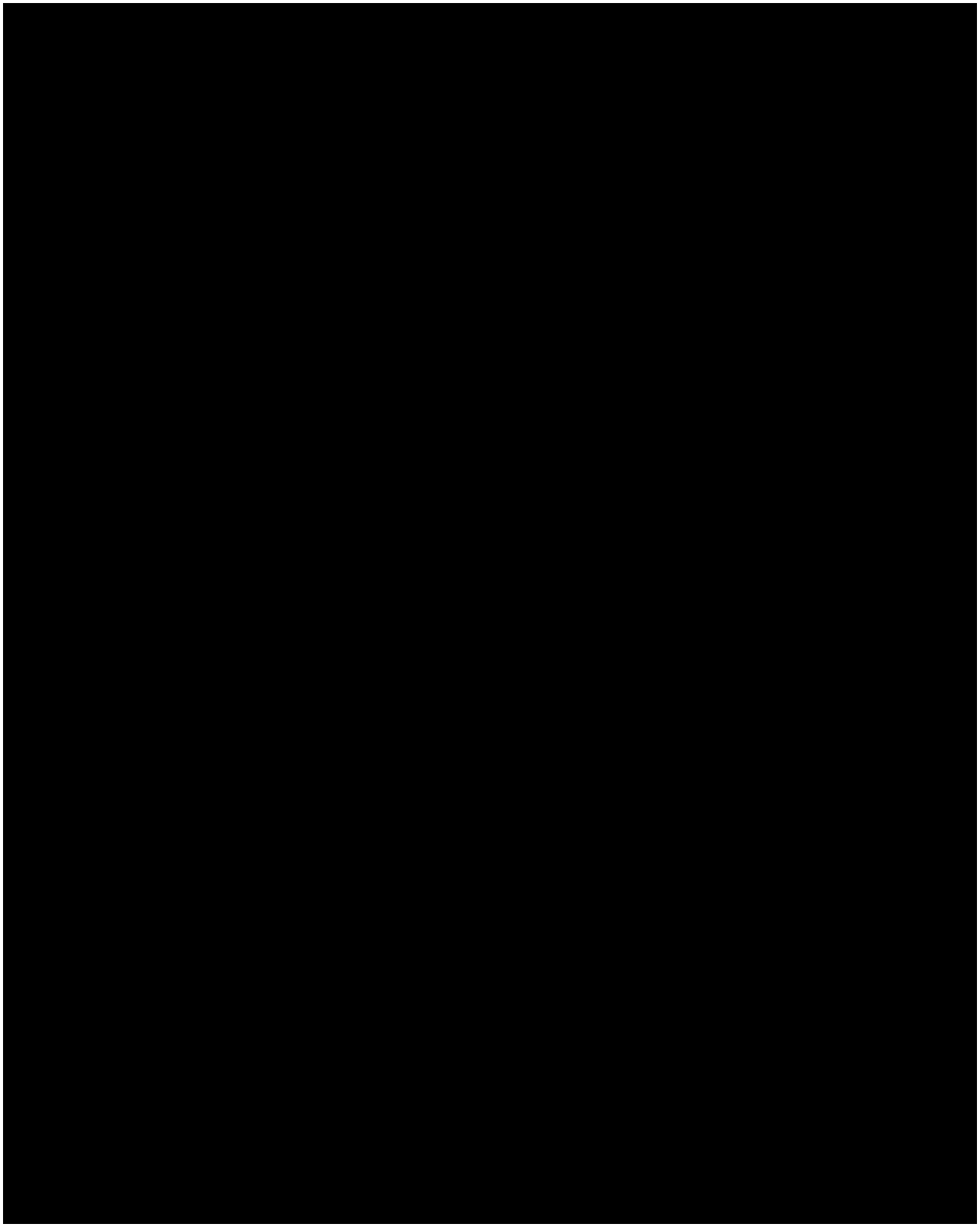
11.1.2. Kinesia ONE™ Accelerometer Score

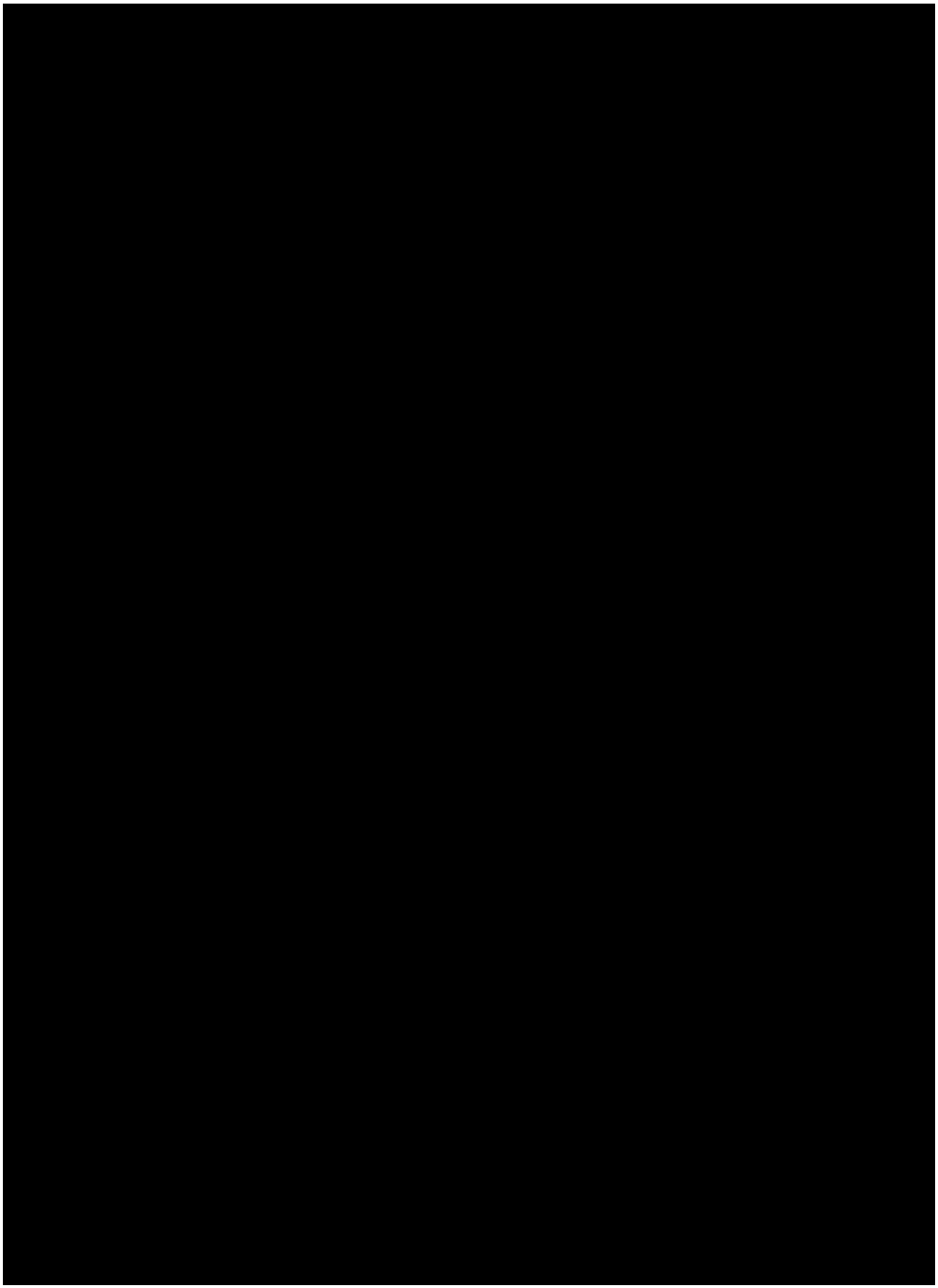
Kinesia ONE™ is an ISO-certified wireless motion sensor worn distally on the index finger, which utilizes 3 orthogonal accelerometers and 3 orthogonal gyroscopes to monitor 3-dimensional motion. Data is transmitted wirelessly from the sensor to a Bluetooth technology-enabled device to use with the Kinesia ONE software (eg, Apple iPad or similar device with preinstalled Kinesia ONE software). The device has received FDA clearance.

Via the Kinesia ONE software application, measures of 3-dimensional motion are converted to scores ranging from 0 to 4, per assessed maneuver; higher scores indicate greater tremor severity. Motion in both arms is captured.

Participants will complete this assessment at each clinic visit as specified in the Schedule of Assessments (Table 2).







[redacted]

11.3. Other Patient-Reported Assessments

11.3.1. Patient Perception of Response Burden

The Patient Perception of Response Burden Questionnaire is a patient-reported measure that assesses the multidimensional construct of response burden (Atkinson 2019).

Participants respond to 6 items assessing 1) how well the questions related to their actual concerns, 2) how comfortable the participants were with answering the questions, 3) how well the survey characterized their health and well-being, 4) the length of time to complete the questionnaires, 5) whether questions seemed unimportant or repetitive, and 6) what additional information should have been gathered. Items 1 to 3 are assessed on a 0 to 10 scale, item 4 is assessed on a 1 to 3 scale, and items 5 and 6 are open-ended. Items 1 and 4 are reverse scored. A composite score can be calculated to create a weighted representative index of relevance, comfort, and well-being relative to time to completion (ie, items 1, 2, and 3 were summed and multiplied by item 4) for a range of 0 to 72, with higher scores indicative of elevated endorsed response burden. The open-ended items will be summarized thematically. The Patient Perception of Response Burden Questionnaire will be performed as specified in the Schedule of Assessments (Table 2).

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

All assessments will be conducted according to the Schedule of Assessments (Table 2).

12.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, ethnicity) and a full medical history will be documented. Whether the participant is left-handed or right-handed will be recorded. This must also additionally include participant recall of history of ET, disease duration, past treatments used, and responsiveness to alcohol and/or other treatments with use intended as off-label treatment of ET (eg, primidone or similar therapies).

12.1.2. Weight and Height

Height and weight will be measured and documented. Body mass index (BMI) will be calculated and documented.

12.1.3. Physical Examination

Whenever possible, the same individual should perform all physical examinations. Physical examinations will include assessment of body systems (eg, head, eye, ear, nose and throat; heart; lungs; abdomen; and extremities) as well as cognitive and neurological examination and MSE. Unscheduled physical examinations may also be conducted per the Investigator's discretion.

Any abnormality in physical examinations will be interpreted by an investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents.

12.1.4. Vital Signs

Vital signs comprise blood pressure and heart rate (supine and standing), respiratory rate, and temperature. Systolic and diastolic blood pressure and heart rate are to be measured after the participant has been supine for at least 5 minutes and then repeated 1 minute and 3 minutes after standing.

Vital signs are measured once at each timepoint with the exception of predose on Day 1, when blood pressure and heart rate are measured supine and standing in triplicate at least 15 minutes apart.

Any abnormality in vital signs will be interpreted by an Investigator as abnormal, NCS; or abnormal, CS in source documents.

12.1.5. Electrocardiogram

A 12-lead ECG will be performed. The standard intervals (heart rate, PR, QRS, QT, and QTcF) as well as any rhythm abnormalities will be recorded.

Electrocardiograms will be performed after the participant has been resting in a supine position for at least 5 minutes. When ECG measurements coincide with safety assessments, vital signs assessment or blood draws, procedures should be carried out in said order (vital signs, ECG, blood draw).

All abnormal ECGs will be interpreted by an investigator as abnormal, NCS, or abnormal, CS in source documents.

12.1.6. Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected. Analytes to be evaluated are summarized in Table 4.

Table 4: Summary of Clinical Laboratory Analytes

Biochemistry	*Renal Panel*: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate *Hepatic Panel*: albumin, ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, total protein, lactate dehydrogenase, gamma glutamyl transferase *Other*: triglycerides, cholesterol (low density lipoprotein [LDL], high density lipoprotein [HDL]), creatine phosphokinase, thyroid stimulating hormone (TSH)
Coagulation	activated partial thromboplastin time, prothrombin time, and international normalized ratio
Hematology	red blood cell count, hemoglobin, hematocrit, white blood cell count with differential, platelet count, and if red blood count indices are abnormal, reflex red blood cell morphology as indicated
Urinalysis	protein, glucose, pH, blood, leukocyte esterase, urobilinogen, bilirubin, ketones, nitrite

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, NCS; or abnormal, CS in source documents.

Follicle stimulating hormone testing will be conducted to confirm whether a participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal (Section 8.1).

12.1.6.1. Drugs of Abuse, Alcohol, Nicotine (Cotinine)

A urine sample will be collected for assessment of the following selected drugs of abuse per the Schedule of Assessments (Table 2): amphetamines, barbiturates, benzodiazepines, cannabinoids/THC, cocaine, methadone, MDMA, methamphetamines, opiates, oxycodone, tricyclic antidepressants, and PCP.

Urine samples will be collected and tested for cotinine. Either urine dipstick or breathalyzer will be used for alcohol testing.

12.1.6.2. Pregnancy Screen

A serum pregnancy test will be conducted for all female participants at Screening; subsequently, a urine pregnancy test will be conducted for all participants of childbearing potential as specified in the Schedule of Assessments (Table 2).

[redacted]

12.1.9. Safety Phone Call

A phone call will be conducted once per week, preferably mid-week in between clinic visits (as specified in Table 2), and again at Day 35, to collect information about current health status, general well-being, IP compliance, or to gather other pertinent health-related information as per investigator judgement.

12.2. Adverse Events and Serious Adverse Events

12.2.1. Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

A TEAE is defined as an AE with onset after the start of IP, or any worsening of a preexisting medical condition/AE with onset after the start of IP and throughout the study. The term IP includes any Sage IP, a comparator, or a placebo administered in a clinical trial.

Laboratory abnormalities [redacted] are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to

be clinically significant. Any abnormalities that meet the criteria for an SAE should be reported in an expedited manner. Laboratory abnormalities [redacted] that are clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

All AEs that occur after any participant has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be reported to Sage Therapeutics.

Participants who discontinue the IP due to an AE, regardless of investigator-determined causality, should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant. Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The sponsor or its representative retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.2. Serious Adverse Event (SAE) Definition

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Places the participant at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

An SAE may also be any other medically important event that, in the opinion of the Investigator may jeopardize the participant or may require medical intervention to prevent 1 of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

All SAEs that occur after any participant has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE report form provided by Sage Therapeutics. Any SAE that is ongoing when the participant completes their final study visit, will be followed by the investigator until the event has resolved, stabilized, returned to baseline status, or until the participant dies or is lost to follow up.

A prescheduled or elective procedure or routinely scheduled treatment will not be considered an SAE, even if the participant is hospitalized. The site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or on a waiting list to be scheduled) prior to obtaining the participant's consent to participate in the study.

- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress, in the opinion of an Investigator, between the participant's consent to participate in the study and at the time of the procedure or treatment.

12.2.3. Definition of Adverse Events of Special Interest

There are no known adverse events of special interest as of the date of signature approval of this clinical protocol.

12.2.4. Relationship to Investigational Product

The investigator must make the determination of relationship to the IP for each AE (not related, related). The following definitions should be considered when evaluating the relationship of AEs and SAEs to the IP.

Not Related	An AE will be considered "not related" to the use of the IP if there is not a reasonable possibility that the event has been caused by the IP. Factors pointing towards this assessment include but are not limited to: the lack of temporal relationship between administration of the IP and the event, the presence of biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE
Related	An AE will be considered "related" to the use of the IP if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point towards this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of alternative explanation for the AE

12.2.5. Recording Adverse Events

AEs spontaneously reported by the participant 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. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, outcome and seriousness (if applicable), and whether or not it caused the participant to discontinue the IP or withdraw early from the study.

Intensity will be assessed according to the following scale:

- Mild: symptom(s) barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s)

- Moderate: symptom(s) of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptom(s) may be needed
- Severe: symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with IP; treatment for symptom(s) may be given and/or participant hospitalized

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2.2. An AE of severe intensity may not necessarily be considered serious.

12.2.6. Reporting Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE(s), the study site must notify Sage or designee within 24 hours of the study site staff becoming aware of the SAE(s). The investigator must complete, sign and date the SAE report form, verify the accuracy of the information recorded on the SAE report form with the corresponding source documents, and send a copy to Sage or designee.

Additional follow-up information, if required or available, should all be sent to Sage or designee within 24 hours of receipt on a follow-up SAE report form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

SAEs occurring after the designated follow up time for the study, should be reported to Sage or designee according to the timelines noted above only if the investigator considers the SAE related to IP.

Sage, or designee, is responsible for notifying the relevant regulatory authorities of certain events. It is the principal investigator's responsibility to notify the IRB/EC of all SAEs that occur at his or her site. Investigators will also be notified of all suspected unexpected serious adverse reactions (SUSARs) that occur during the clinical study. Each site is responsible for notifying its IRB of all SUSARs.

In addition, appropriate personnel in Sage Drug Safety and Pharmacovigilance or designee will unblind SUSARs for the purpose of regulatory reporting. Sage or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Sage, or designee, will submit SUSARs to investigators in a blinded fashion.

12.3. Pregnancy

If a participant becomes pregnant after the first administration of IP, pregnancy information must be collected and recorded on the pregnancy form and submitted to the sponsor within 24 hours of learning of the pregnancy. Details will be collected for all pregnancies for which conception was likely to have occurred after the start of IP administration until 5 terminal half-lives following the last administration of IP or until the completion of the study whichever is longer. Any pregnancy occurring in that time frame will be followed until delivery or termination of the pregnancy. The investigator will also attempt to collect pregnancy information on any participant's partner who becomes pregnant after the participant has received the first

administration of IP. After obtaining the necessary signed informed consent from the pregnant partner directly, the investigator will follow the same pregnancy reporting procedures specified for pregnant participants.

The participant or participant's partner will be followed to determine the outcome of the pregnancy. The outcome of all pregnancies (eg, spontaneous abortion, elective abortion, normal birth) must be followed and documented even if the participant was discontinued from the study. The investigator will collect follow-up information on the participant or participant's partner and the neonate, and the information will be forwarded to Sage or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication. Any complication during pregnancy (eg, anemia, infections, preeclampsia) should be reported as an AE/SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death), the investigator should follow the procedures for reporting an SAE.

12.4. Overdose

An overdose is any dose of study treatment given to a participant or taken by a participant that exceeds more than one extra tablet within 24 hours as described in protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded.

13. STATISTICS

Detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock. Any changes or additions to the SAP following database lock will be described in detail in the clinical study report.

13.1. Data Analysis Sets

The Randomized Set will include all participants who are randomized.

The Safety Set will include all participants administered IP.

The Full Analysis Set will include all randomized participants who received any amount of IP and have a baseline and at least one postbaseline TETRAS performance subscale part 4 upper limb tremor score.

[redacted]

The Per Protocol Set will include all participants in the Full Analysis Set without any major protocol deviations that could affect efficacy. The review of major protocol deviations will be completed, and the decision on whether the deviation affects efficacy will be documented before database unblinding. Note that a positive cotinine test on Days 1, 8, 15, 22 or 29 constitutes a major protocol deviation.

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All participants will be used in the analyses, as per the analysis populations, using all nonmissing data available. No imputation process will be used to estimate missing data.

13.3. General Considerations

All participant data, including those that are derived, that support the tables and figures will be presented in the participant data listings. Some data may be presented only in participant data listing, some may be presented with a corresponding table or figure; these will be indicated in relevant sections below. Participants will be summarized according to treatment received.

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to receipt of IP.

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

13.4. Demographics and Baseline Characteristics

Demographic data, such as age, race, and ethnicity, and baseline characteristics, such as height, weight, and BMI, will be summarized using the Safety Set.

Pregnancy test results and drug screen results will be listed but not summarized.

Medical history will be listed by participant.

13.5. Efficacy Analysis

The estimand for the primary efficacy analysis is the treatment difference between SAGE-324 and placebo in mean change from baseline in clinic-based TETRAS performance subscale part 4 upper limb tremor scores at Day 29 based on the Full Analysis Set. This will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline TETRAS performance subscale part 4 upper limb tremor score, assessment timepoint, and timepoint-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline clinic visits will be included in the model. The main comparison will be between SAGE-324 and placebo at the 29-day timepoint. Model-based point estimates (ie, least squares means, 5% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz compound symmetry or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not UN, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

Similar to those methods described above for the primary endpoint, an MMRM will be used for the analysis of the change from baseline in TETRAS total performance scores, Kinesia ONE accelerometer scores and TETRAS ADL scores.

Other efficacy analyses will be specified in the SAP. In general, data will be analyzed using appropriate descriptive statistics or prespecified statistical methods as applicable; participant listings will be provided for all efficacy data. Participants will be analyzed according to randomized treatment for the purpose of efficacy unless otherwise specified.

Sensitivity analyses will be described in the SAP.

13.6. Safety Analyses

Safety and tolerability of SAGE-324 will be evaluated by AEs, concomitant medication usage, [redacted] Safety data will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Set using treatment received.

13.6.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or higher. A treatment-emergent adverse event (TEAE) is defined as an AE with onset after the first dose of IP. The analysis of AEs will be based on the concept of TEAEs. The incidence of TEAEs will be summarized by System Organ Class (SOC) and preferred term. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to IP.

Any TEAEs leading to discontinuation of treatment or withdrawal from the study and any treatment-emergent SAEs will be summarized.

All AEs and SAEs (including those with onset or worsening before the start of IP) through the end of the study will be listed.

[redacted]

13.6.3. Physical Examinations

The occurrence of a physical examination, including MSE, (yes/no) and the date performed will be listed by participant.

[redacted]

13.6.6. 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 (WHO-DD) September 2015, or later.

All medications taken within 30 days prior to informed consent through the duration of the study will be recorded. In addition, all psychotropic medications taken in the previous 30 days prior to screening will be recorded. Those medications taken prior to the initiation of the start of IP will be denoted “Prior”. Those medications taken prior to the initiation of the IP and continuing beyond the initiation of the IP or those medications started at the same time or after the initiation of the IP will be denoted “Concomitant”.

Medications will be presented according to whether they are “Prior” or “Concomitant” as defined above. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Details of prior and concomitant medications will be listed by participant, start date, and verbatim term.

13.8. Sample Size and Power

The sample size of this study is based on the assumption of a 3 points difference in the change from baseline TETRAS performance subscale part 4 upper limb tremor score between SAGE-324 and placebo with a standard deviation of 3.5 points. Under these assumptions, a sample size of 25 evaluable participants per group would provide 85% power for detecting a placebo-adjusted treatment difference of 3 points in TETRAS performance subscale part 4 upper limb tremor score assuming a 2-sided test at an alpha level of 0.05. By including 2 treatment groups and using a 1:1 randomization, a total of 50 evaluable participants are required. Assuming a nonevaluability rate of 15%, approximately 60 participants will be randomized. Additional participants may be enrolled if the dropout rate is greater than 15%.

13.8.1. Interim and Data Monitoring Committee (DMC) Analyses

13.8.1.1. Interim Analysis

The sponsor may conduct an interim analysis. Detailed descriptions of planned data analyses will be provided in a separate interim statistical analysis plan (SAP), if applicable.

13.8.1.2. DMC Analysis

Not applicable

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Sage Therapeutics will visit the investigational study site per Sage SOPs to:

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

During the study, a monitor from Sage Therapeutics or representative 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 case report forms, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the participant'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 participant (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or EC.

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

14.2. Audits and Inspections

Sage Therapeutics or authorized representatives of Sage Therapeutics, a regulatory authority, or an independent EC or an IRB may visit the site to perform an audit(s) or inspection(s), including source data verification. The purpose of a Sage Therapeutics audit or a regulatory authority 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/ICH GCP guidelines, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency or IRB/EC about an inspection.

14.3. Institutional Review Board or Ethics Committee

The principal investigator must obtain IRB (or EC) approval for the clinical study prior to enrolling a participant. Initial IRB (or EC) approval, and all materials approved by the IRB (or EC) for this study including the participant consent form and recruitment materials must be maintained by the investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practice and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit(s) at the clinical site. Please see Section 14.2 for more details regarding the audit process.

The investigator must have adequate quality control practices to ensure that the study is performed in a manner consistent with the protocol, GCP/ICH GCP guidelines, and applicable regulatory requirements. The investigator is responsible for reviewing all identified protocol deviations. Significant protocol deviations should be reported to the IRB/EC per the IRB/EC's written procedures.

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. When the investigator retains the services of any individual or party to perform trial-related duties and functions, the investigator must ensure the individual or party is qualified to perform trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed, and any data generated.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained, if necessary, to provide clarification.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF, must be given a written and dated approval or favorable opinion by an IRB or EC as appropriate. The investigator must obtain and document approval before he or she can enroll any participant into the study. The IRB or EC must supply to the sponsor a list of the IRB/EC membership and a statement to confirm that the IRB/EC is organized and operates according to GCP and applicable laws and regulations.

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

The principal investigator is also responsible for providing the IRB or EC with reports of any reportable serious adverse drug reactions from any other study conducted with the IP. Sage Therapeutics will provide this information to the principal investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or EC according to local regulations and guidelines. In addition, the principal investigator must inform the IRB/EC and sponsor of any changes significantly affecting the conduct of the trial and/or increasing the risk to participants (eg, violations to the protocol or urgent safety measures taken for participant safety).

16.2. 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 are consistent with ICH and GCP guidelines, as well as all applicable regional or national regulatory requirements.

16.3. Written Informed Consent

Prior to enrolling a trial participant, the investigator(s) will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and allowed time to consider the information provided.

When the participant decides to participate in the trial, the participant (or the participant's, parent or legally authorized representative) must provide signed and dated informed consent. The written consent must be obtained before conducting any study procedures. The investigator must document the consent process in the participant's source records. The investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant or to the participant's parent or legally authorized representative.

Throughout the trial participants should be informed of any changes made to the study and as new safety and or risk information becomes known. The provision of this information will be documented in the participant's source records, and when applicable, an updated ICF will be provided.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Sage Therapeutics or its representative(s) will be allowed to conduct site visits at the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the facility, drug storage area, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

Inspection of the study by a regulatory authority may occur at any time. The investigator must agree to the inspection of study-related records and source documents by the regulatory authority representative(s).

17.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for the period outlined in the site contract, or for a period of 2 years after the last marketing application approval, and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Sage is responsible to inform the investigator/institution as to when study documents no longer need to be retained.

18. PUBLICATION POLICY

All information concerning SAGE-324 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.

19. LIST OF REFERENCES

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A PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY EVALUATING THE EFFICACY, SAFETY, AND TOLERABILITY OF SAGE-324 IN THE TREATMENT OF INDIVIDUALS WITH ESSENTIAL TREMOR

324-ETD-201

Investigational Product	SAGE-324 Oral Tablet
Clinical Phase	Phase 2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted], MD
Sponsor Medical Monitor	[redacted], MD, PhD
Date of Original Protocol	23 October 2019
Date of Amendment 1	20 December 2019
Date of Amendment 2	24 February 2020
Date of Amendment 3	10 June 2020

SPONSOR APPROVAL

Protocol Number: 324-ETD-201

Study Title: A Phase 2, Double-Blind, Placebo-Controlled, Randomized Study Evaluating the Efficacy, Safety, and Tolerability of SAGE-324 in the Treatment of Individuals with Essential Tremor

Protocol Version and Date: Version 4, 10 June 2020

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INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for SAGE-324. I have read the 324-ETD-201 protocol 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 (DD/MMM/YYYY)

CONTACT INFORMATION

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Sage Study Physician	[redacted], MD	Phone [redacted]
Sage Medical Monitor	[redacted], MD, PhD	Mobile: [redacted] Office phone: [redacted] E-mail: [redacted]
CRO Medical Monitor and 24-Hour Emergency Contact	[redacted], MD, MPH	[redacted] Phone: [redacted] E-mail: [redacted]
SAE Reporting Information	IQVIA Lifecycle Safety	4820 Emperor Boulevard Durham, NC 27703 E-mail: Sage.Safety@iqvia.com Fax: +1-855-638-1674 SAE Hotline: +1-855-564-2229
Product Complaints	Sage Therapeutics, Inc.	E-mail: productcomplaints@sagerx.com Phone: +1-833-554-7243

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics, Inc. (hereafter referred to as Sage Therapeutics, or Sage)

Name of Investigational Product:
SAGE-324 Oral Tablet

Name of Active Ingredient:
SAGE-324

Title of Study:
A Phase 2, Double-blind, Placebo-controlled, Randomized Study Evaluating the Efficacy, Safety, and Tolerability of SAGE-324 in the Treatment of Individuals with Essential Tremor

Number of Sites and Study Location: This study will take place at approximately 30 sites in the United States.

Phase of Development: Phase 2

Planned Duration for each Study Participant:
The duration of participation (from Screening through the final follow-up visit) for each participant is estimated to be up to 71 days.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the effect of SAGE-324 compared to placebo on upper limb tremor reduction in individuals with essential tremor (ET) after 28 days of treatment	Change from baseline compared to placebo in The Essential Tremor Rating Assessment (TETRAS) performance subscale part 4 upper limb tremor score on Day 29
Secondary	
To assess the effect of SAGE-324 compared to placebo on overall upper limb tremor reduction	• Change from baseline compared to placebo in TETRAS performance subscale part 4 upper limb tremor score at all other timepoints • Change from baseline compared to placebo in Kinesia ONE accelerometer scores
To assess the effect of SAGE-324 compared to placebo on activities of daily living (ADLs)	• Change from baseline compared to placebo in TETRAS Scale ADL score
To assess the effect of SAGE-324 compared to placebo on overall tremor	• Change from baseline compared to placebo in TETRAS total performance score
To evaluate the safety and tolerability of SAGE-324	• Incidence of treatment-emergent adverse events (TEAEs)

[redacted]

Study Description:

This is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of SAGE-324 in individuals with ET. Participants, site staff, and sponsor personnel will be masked to treatment allocation.

This study includes a Screening Period of up to 28 days, a 29-day treatment period (28 days of dosing), and a 14-day follow up period. After providing informed consent, participants will undergo screening assessments as outlined in Table 2 to determine eligibility.

Screening Period: The Screening Period begins with the signing of the informed consent form (ICF). Eligible participants will visit the study center on Day 1 and complete additional eligibility and baseline assessments, as specified in the Schedule of Assessments (Table 2). Following completion of screening

and Day 1 eligibility checks, participants will be randomized to 1 of 2 treatment groups (SAGE-324 60 mg daily, or placebo) in a 1:1 ratio.

Double-Blind Treatment Period: Starting on Day 1, participants will receive a single dose of investigational product (IP) once daily for 28 days on an outpatient basis, to be taken in the morning with food that comprises a minimum of 400 calories. Doses occurring on scheduled clinic visits will be administered in the clinic, and doses occurring on all other days will be self-administered by the participant at home. During the Treatment Period, participants will return to the study center approximately once per week for efficacy and safety assessments as specified in Table 2. Participants will be trained on the use of software applications and devices necessary to complete questionnaires or other assessments. During the study, a phone call will be conducted once per week, preferably midway between clinic visits, to review current status of participant.

Follow-Up Period: Follow-up visits will be conducted on an outpatient basis. Participants will continue to complete questionnaires as indicated in Table 2 and will receive a phone call approximately 7 days after the last dose of IP (ie, Day 35) for safety monitoring. Participants will return to the study center for an end of study visit approximately 14 days following the last dose of IP (ie, Day 42).

Number of Participants (planned): Approximately 60 participants, with approximately 30 per arm.

Eligibility Criteria:

Inclusion Criteria:

1. Participant has signed an ICF before any study-specific procedures or washout of drugs is performed.
2. Participant is ambulatory and is 18 to 80 years of age, inclusive, at the time informed consent is obtained.
3. Participant has a diagnosis of ET, as defined by all of the following criteria:
   a. Isolated tremor syndrome consisting of bilateral upper limb action tremor
   b. At least 3 years duration
   c. With or without tremor in other locations (eg, head, voice, or lower limbs)
   d. Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism, isolated focal tremors (eg, voice, head), task- and position-specific tremors, sudden tremor onset or evidence of stepwise deterioration of tremor
4. Participant scores at least 1.5 for each of the six items that comprise the combined total upper limb TETRAS (total performance subscale part 4) with the total score for the dominant upper limb (the sum of the 3 items for either the right or left upper limb, whichever is dominant) being at least 5.5, at both Screening and predose on Day 1.
5. Participant is willing to discontinue medications taken for the treatment of ET within 14 days or 5 half-lives (whichever is longer) prior to receiving IP. Medications taken for the treatment of ET that were discontinued prior to receiving IP may be resumed following Day 29.
6. Participant is willing to discontinue the use of alcohol and products that contain nicotine within at least 1 week prior to Day 1 and through Day 29 of the study.
7. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral

salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does include abstinence).

8. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 13 weeks after receiving study drug, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
9. Male participant is willing to abstain from sperm donation for the duration of the study and for 13 weeks after receiving study drug.
10. Participant has no clinically significant findings, as determined by the investigator, on Screening and predose Day 1 physical examination including mental state examination (MSE) and neurologic examination, 12-lead ECG, or screening clinical laboratory tests.

Exclusion Criteria:

1. Participant has presence of known causes of enhanced physiological tremor.
2. Participant has had recent exposure (14 days prior to Day 1) to tremorgenic drugs or presence of alcohol withdrawal state.
3. Participant has had direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor.
4. Participant has had a previous procedure for the treatment of ET, deep brain stimulation, brain lesioning, or magnetic resonance (MR) guided procedure, eg, MR-guided focused ultrasound.
5. Participant has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.)
6. Participant has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic (hypothyroidism with stable thyroid replacement is acceptable), or oncological disease.
7. Participant has history of substance abuse prior to Screening, has a positive screen for drugs of abuse at Screening or predose on Day 1, or has a positive screen for alcohol predose on Day 1.
8. Participant has a known allergy to SAGE-324 or any excipient.
9. Participant has had exposure to another investigational drug or device within 30 days or 5 half-lives (if known) of the investigational drug, whichever is longer, prior to the Day 1 visit.
10. Participant has history of suicidal behavior within 2 years or answers “YES” to questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk of suicide in the opinion of the investigator.
11. Participant has donated one or more units (1 unit = 450 mL) of blood or experienced acute loss of an equivalent amount of blood within 60 days prior to Day 1.
12. Participant has any condition or comorbidity that in the opinion of the investigator would limit or interfere with the participant’s ability to complete or partake in the study.
13. Participant is unwilling or unable to comply with study procedures and required training.

14. Participant has used any known moderate or strong cytochrome P450 3A4 inhibitors and/or inducers within 14 days or 5 half-lives (whichever is longer) prior to Day 1 or consumed grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St. John's Wort or products containing these within 30 days prior to Day 1. Use of mild cytochrome inhibitors and/or inducers may be permitted.
15. Participant has concurrent or recent exposure (14 days or five half-lives, whichever is longer, prior to the Day 1 visit) to sedative/hypnotic drugs, stimulants, highly caffeinated beverages or dietary supplements containing high doses of caffeine, or recent increase above regular daily consumption of caffeine.
16. Participant plans to undergo elective surgery or relocate during participation in the study.
17. Participant is investigative site personnel or a member of their immediate families (spouse, parent, child or sibling whether biological or legally adopted).
18. [Removed]
19. Female participant has a positive pregnancy test or confirmed pregnancy.

Investigational Product Dosage and Mode of Administration:

SAGE-324 (60 mg) or matched placebo oral tablets will be administered in the clinic or self-administered once daily, in the morning, at approximately the same time each day, with food that comprises a minimum of 400 calories.

Duration of Treatment:

Each participant will receive a single dose of SAGE-324 oral tablets or matching placebo administered once daily for 28 days.

Statistical Methods:

A separate statistical analysis plan (SAP) will provide a detailed description of the data analyses to be performed in the study. The SAP will be finalized and approved prior to database lock.

General Considerations

For the purpose of all efficacy and safety analyses where applicable, baseline is defined as the last measurement prior to the start of IP administration.

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

Analysis Sets

The Randomized Set is defined as all participants who are randomized.

The Safety Set will include all participants who were administered IP.

The Full Analysis Set will include all randomized participants who received any amount of IP and have a baseline and at least one postbaseline TETRAS performance subscale part 4 upper limb tremor score.

[redacted]

The Per Protocol Set will include all participants in the Full Analysis Set without any major protocol deviations that could affect efficacy. The review of major protocol deviations will be completed, and the decision on whether the deviation affects efficacy will be documented before database unblinding.

Determination of Sample Size

The sample size of this study is based on the assumption of a 3-point difference in the change from baseline TETRAS performance subscale part 4 upper limb tremor scores between SAGE-324 and placebo with a standard deviation of 3.5 points. Under these assumptions, a sample size of 25 evaluable participants per group would provide 85% power for detecting a placebo-adjusted treatment difference of 3 points in TETRAS performance subscale part 4 upper limb tremor score, assuming a 2-sided test at an alpha level of 0.05. By including 2 treatment groups and using a 1:1 randomization, a total of 50 evaluable participants are required. Assuming a nonevaluability rate of 15%, approximately 60 participants will be randomized. Additional participants may be enrolled if the drop-out rate is higher than 15%.

Analysis of Primary Efficacy Endpoint

The estimand for the primary efficacy analysis is the treatment difference between SAGE-324 and placebo in mean change from baseline in clinic-based TETRAS performance subscale part 4 upper limb tremor score at Day 29 based on the Full Analysis Set. This will be analyzed using a mixed-effects model for repeated measures (MMRM); the model will include treatment, baseline TETRAS performance subscale part 4 upper limb tremor score, assessment timepoint, and timepoint-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline clinic visits will be included in the model. The main comparison will be between SAGE-324 and placebo at the 29-day timepoint. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz compound symmetry or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not unstructured, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

Analysis of Secondary Efficacy Endpoints

Similar to those methods described above for the primary endpoint, an MMRM will be used to analyze of the change from baseline in TETRAS total performance scores, Kinesia ONE accelerometer scores and TETRAS ADL scores. Individual items of the TETRAS subscales will be summarized.

Safety Analysis

Safety and tolerability of study drug will be evaluated by incidence of TEAEs/serious adverse events,

[redacted]

Interim Analysis

The sponsor may conduct an interim analysis. Detailed descriptions of planned data analyses will be provided in a separate interim statistical analysis plan (SAP), if applicable.

Table 2: Schedule of Assessments

Assessment	Screening	Treatment Period									Follow-up Period	
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15(±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**35 (±1) Safety Phone Call**	**42 (±1) EOS/ETV**
Informed Consent	X											
Inclusion/Exclusion	X	X										
Demographics	X											
Medical History	X											
Pregnancy Test	X (serum; all women)	X (urine; WOCBP only)				X (urine; WOCBP only)				X (urine; WOCBP only)		X (urine; WOCBP only)
FSH (postmenopausal women only)	X											
Randomization[a]		X										
Alcohol/cotinine screens		X		X		X		X		X		
Drug screen	X	X										
Physical examination[b]	X	X		X		X		X		X		X
Neurological examination including MSE[b]	X	X		X		X		X		X		X
Body height	X											
Body weight	X											
Vital signs[c]	X	X		X		X		X		X		X
12-Lead ECG[d]	X	X		X		X		X		X		X
Chemistry/hematology/ coagulation/urinalysis	X	X		X		X		X		X		X
[redacted]												

Assessment	Screening	Treatment Period									Follow-up Period	
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15(±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**35 (±1) Safety Phone Call**	**42 (±1) EOS/ETV**
[redacted]												
Kinesia ONE[f]	X	X		X		X		X		X		X
TETRAS[g]	X	X		X		X		X		X		X
[redacted]												

Assessment	Screening	Treatment Period									Follow-up Period	
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15(±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**35 (±1) Safety Phone Call**	**42 (±1) EOS/ETV**
Patient Perception of Response Burden										X		X
[redacted]												
Participant training[h]	X	X										
Dispense study drug		X		X		X		X				
IP administration		Administered once daily for 28 days							Not applicable			
AEs/SAEs	X											
Prior and concomitant medication and history[i]	X											

Abbreviations: ADL = activities of daily living; AE = adverse event; [redacted]; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; [redacted]; ETV = early termination visit; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; ICF = informed consent form; min = minutes; IP = investigational product; MSE = mental state examination; [redacted]; SAE = serious adverse event; TETRAS = The Essential Tremor Rating Assessment Scale; WOCBP = women of childbearing potential

Notes:

- The suggested order of assessments during clinic visits is: vital signs, TETRAS, Kinesia ONE, ECG, blood sample collection for [redacted] and clinical laboratory assessments, and questionnaires.
- All assessments will be performed predose unless specified in a footnote.

[a] Randomization will occur on Day 1 after meeting all eligibility criteria.

[b] Complete physical examinations (including MSE and comprehensive neurologic examination) should be performed as specified and additionally as clinically necessary (see Section 12.1.3).

[c] Predose on Day 1, supine and standing blood pressure and heart rate will be collected in triplicate at least 15 minutes apart, measured after the participant has been in the supine position for at least 5 minutes and then repeated 1 minute and 3 minutes after standing. Respiratory rate and temperature are collected once predose on Day 1. Vital signs will be collected once predose at all other visits. All postdose vital signs will be collected once at approximately 3 hours (±60 min) after dosing.

[d] ECGs will be collected and read centrally. ECGs will be performed predose and approximately 3 hours (±60 min) postdose. All ECGs must be performed after the participant has been in a supine position for at least 5 minutes.

[e] [redacted]

[f] Kinesia ONE will be assessed subsequently to TETRAS Performance subscale part 4 upper limb tremor.

[g] The TETRAS Performance and TETRAS ADL subscales will be assessed at Screening and predose at each clinic visit. The TETRAS Performance subscale part 4 upper limb tremor will be assessed before Kinesia ONE. In addition, on Day 15, the TETRAS Performance subscale will be assessed at 5 and 8 hours (±30 min) postdose. A videographer will record each TETRAS administration.

[h] Participants will be trained by study personnel on the use of software applications, Investigational Product Diary, and devices necessary for the conduct of the study.

[i] Prior medications will be recorded during Screening and will include all medications and supplements taken within the 30 days prior to signing the ICF through the first dose of IP, as well as a complete history of all treatments for ET since the year of diagnosis. Concomitant medications will be recorded thereafter throughout the duration of the study.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ADL	activities of daily living
AUC_{inf}	area under the curve from 0 to infinity
$AUC_{0\text{-}tau}$	area under the concentration-time curve from 0 to end of the dosing period
BMI	body mass index
[redacted]	[redacted]
C_{max}	maximum observed concentration
CRO	contract research organization
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End-of-Study
[redacted]	[redacted]
[redacted]	[redacted]
ET	essential tremor
[redacted]	[redacted]
ETV	early termination visit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
PD	pharmacodynamic
[redacted]	[redacted]
PI	principal investigator
PK	pharmacokinetic

Abbreviation	Definition
[redacted]	
PV	Pharmacovigilance
QTcF	QT corrected according to Fridericia's formula
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
t_{max}	time of occurrence of C_{max}
WHO	World Health Organization

5. INTRODUCTION

SAGE-324 is a positive allosteric modulator (PAM) of A-type γ-aminobutyric acid-gated chloride channel ($GABA_A$) receptors, the major class of inhibitory neurotransmitter receptors in the brain. In addition to being developed as an adjunctive therapy in epilepsy and other seizure disorders under IND 139201, SAGE-324 is also being developed for the treatment of Essential Tremor (ET).

Essential tremor is a permanently debilitating, neurologically determined, common movement disorder characterized by involuntary rhythmic oscillation of a body part due to intermittent muscle contractions typically occurring when not at rest, thus interfering with fine motor skills associated with daily activities (Olanow 2008, Deuschl 2011, Hopfner 2016, NIH 2019). Although the pathophysiology and etiology of ET is not fully understood, it is postulated that approximately 50% of ET patients feature an autosomal dominant pattern of familial inheritance and that non-inherited cases may have toxin-based or other causality (Olanow 2008, Hopfner 2016). ET is the most common movement disorder in the US, with prevalence estimated to be approximately 2.2% of the population, representing a substantial societal medical burden with over an estimated 7 million ET patients in the US alone (Louis 2014).

In general, active tasks of daily life are adversely impacted by ET, including but not limited to speech, handwriting, household tasks, and occupational demands, contributing negatively to psychosocial well-being, general anxiety, and overall quality of life (Koller, 1989). Although benign in term of its effect on life expectancy, ET is a progressive neurodegenerative condition whose symptoms are typically disabling, often forcing patients to change jobs or seek early retirement (Zappia, 2013). In some cases, serious disability may ensue.

The pharmacological profile of SAGE-324 is theorized to induce therapeutic effect in the treatment of ET. Based on preclinical studies of SAGE-324, which features a different mechanism of action than that of propranolol, the pharmacokinetic (PK)/ pharmacodynamic (PD) profile suggests SAGE-324 may safely ameliorate symptoms in patients suffering from ET, regardless of propranolol use.

There are currently ongoing Phase 1 clinical studies of SAGE-324 in healthy adults and in adults with ET. These studies, in addition to preclinical studies of SAGE-324, are detailed in the investigator's brochure.

With a $GABA_A$ receptor-based mechanism of action featuring positive allosteric modulation capability, SAGE-324 represents a novel approach to the treatment of ET, which may help address the unmet medical need of the ET population, warranting further study of SAGE-324 as a potential treatment for this common movement disorder.

Henceforth, this double-blind, placebo-controlled efficacy and safety study of SAGE-324 will be conducted in adults and is designed to assess the effect of SAGE-324 on a variety of outcome measures specific to ET disease characteristics and associated quality of life domains.

5.1. Dose Justification

The dose of SAGE-324 planned for this study is 60 mg given as oral tablets, to be administered once daily in the morning with food. The dose was selected based on preliminary data from 3 active studies of SAGE-324, which included: unblinded data from completed cohorts in

324-CLP-101 Part A (oral solution SAGE-324 doses of 3 mg, 10 mg, 30 mg, 45 mg, 60 mg); Part C (oral solution SAGE-324 doses of 30 mg); Part D (oral suspension SAGE-324 doses of 30 mg) in healthy subjects; and preliminary data from open-label Part E (oral suspension SAGE-324 doses of 45 mg and 60 mg) in participants with ET; additional preliminary data from 324-CLP-102 cohorts 1 through 6 (cohorts 1 to 5 unblinded, cohort 6 blinded), which evaluated oral suspension doses ranging from 5 mg to 60 mg; and preliminary unblinded data from 324-CLP-104, which compared the relative bioavailability of the oral tablet (30 mg) vs oral suspension (30 mg) formulations of SAGE-324 and separately the effect of food on the PK of the SAGE-324 oral tablet. In 324-CLP-101 and 324-CLP-102 studies, doses were administered in a fasted state. The preliminary data from all of these active studies collectively informed the route of administration (oral) and dose strength of 60 mg as oral tablets planned for further evaluation in this study.

SAGE-324 was generally well-tolerated in participants with ET and in healthy volunteers, as was shown in the preliminary data of 324-CLP-101 Part E at single administration doses of 45 mg and 60 mg, and in 324-CLP-102 through once-daily administered doses of up to 60 mg for 14 days. In addition, tremor reduction was observed at both doses on TETRAS and Kinesia ONE accelerometry, with greater improvement seen at 60 mg compared to 45 mg.

In the clinically complete study 324-CLP-104, preliminary data showed that SAGE-324 oral tablets, when coadministered with a meal, resulted in exposures approximately equivalent to that of SAGE-324 oral suspension under fasted conditions. Therefore, the SAGE-324 oral tablets are recommended to be administered with food.

5.2. Benefit/Risk Assessment

Based on the mechanism of action of SAGE-324 and the results of completed nonclinical studies and preliminary data of currently ongoing clinical studies of SAGE-324, it is theorized that participants may have symptomatic amelioration, ie, tremor reduction and possibly improved quality of life from potentially stabilizing disease characteristics associated with ET.

Potential risks anticipated in this study are based on available data from toxicology studies of SAGE-324 in addition to preliminary data from 3 ongoing, currently active Phase 1 clinical studies of SAGE-324.

Available preliminary clinical data are summarized in the SAGE-324 Investigator's Brochure. There have been no deaths or SAEs related to IP, and based on the preliminary clinical data available, there have been no confirmed clinically significant trends in clinical laboratory evaluations, vital signs, or physical examinations.

Based on available preliminary clinical data from SAGE-324 active clinical studies, AEs of somnolence and feeling of relaxation are considered adverse drug reactions. In addition to scheduled clinic visits, the current status of study participants will be reviewed via weekly phone calls, in between clinic visits.

6. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the effect of SAGE-324 compared to placebo on upper limb tremor reduction in individuals with essential tremor (ET) after 28 days of treatment	Change from baseline compared to placebo in The Essential Tremor Rating Assessment (TETRAS) performance subscale part 4 upper limb tremor score on Day 29
Secondary	
To assess the effect of SAGE-324 compared to placebo on overall upper limb tremor reduction	• Change from baseline compared to placebo in TETRAS performance subscale part 4 upper limb tremor score at all other timepoints • Change from baseline compared to placebo in Kinesia ONE accelerometer scores
To assess the effect of SAGE-324 compared to placebo on activities of daily living (ADLs)	• Change from baseline compared to placebo in TETRAS Scale ADL score
To assess the effect of SAGE-324 compared to placebo on overall tremor	• Change from baseline compared to placebo in TETRAS total performance score
To evaluate the safety and tolerability of SAGE-324	• Incidence of treatment-emergent adverse events (TEAEs)
[redacted]	

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of SAGE-324 in individuals with ET. Participants, site staff, and sponsor personnel will be masked to treatment allocation (see Section 9.5).

This study includes a Screening Period of up to 28 days, a 29-day treatment period consisting of 28 days of dosing with the end of treatment visit intended to be on Day 29 at trough, and a 14-day follow-up period relative to final dose (Figure 1). After providing informed consent, participants will undergo screening assessments as outlined in Table 2 to determine eligibility.

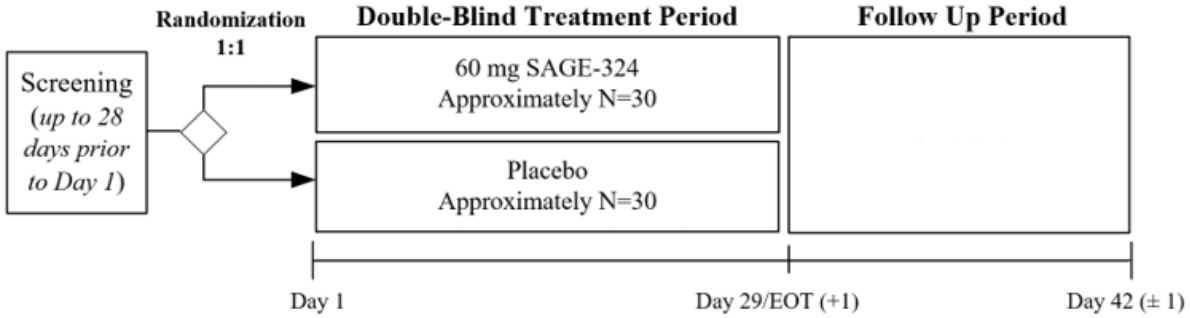
The Screening Period begins with the signing of the informed consent form (ICF). Eligible participants will visit the study center on Day 1 and complete additional eligibility assessments of safety and efficacy, as specified in the Schedule of Assessments (Table 2). Following completion of screening and Day 1 eligibility checks, participants will be randomized to 1 of 2 treatment groups (SAGE-324 60 mg daily, or placebo) in a 1:1 ratio.

During the double-blind Treatment Period, starting on Day 1, participants will receive a single dose of investigational product (IP) once daily in the morning with food for 28 days on an outpatient basis (see Section 10.5). Doses occurring on scheduled clinic visits will be administered in the clinic, and doses occurring on all other days will be self-administered by the participant at home as specified in Table 2. During the Treatment Period, participants will return to the study center approximately once per week for efficacy and safety assessments as specified in Table 2. In addition, a phone call will be conducted once per week, preferably mid-way between clinic visits, to review current status of the participant.

In addition to Kinesia ONE-specific training, clinical study center staff and study participants will be trained on the use of software applications and devices necessary to complete questionnaires or other assessments as required. During in-clinic visits, clinical study center staff will be available to assist participants as needed, to ensure they can access and use the software applications and devices correctly according to the training.

During the follow-up period, visits will be conducted on an outpatient basis. In addition to the phone calls to review current status, participants will receive a phone call approximately 7 days after the last dose of IP (ie, Day 35) for safety monitoring. Participants will return to the study center for an end of study visit approximately 14 days following the last dose of IP (ie, Day 42).

Figure 1: Study Design



Abbreviation: EOT = end of treatment

7.2. Number of Participants

Approximately 60 participants are planned, with approximately 30 participants enrolled per arm, to produce 25 evaluable participants per arm for primary efficacy analysis. Additional participants may be randomized if the drop-out rate is higher than anticipated (ie, >15%).

7.3. Treatment Assignment

Participants will be assigned to IP (active or placebo) in accordance with the randomization schedule on Day 1. Additional details on randomization and blinding are provided in Section 9.5.

7.4. Dose Adjustment Criteria

If participants report adverse events that are considered by the investigator to be related to the IP and not tolerable, the investigator may reduce the dose of IP from 60 mg in 15 mg decrements (ie, 60, to 45, to 30 mg), as medically appropriate. The dose may not be reduced below 30 mg: if intolerable adverse events persist at the 30 mg dose, the IP should be permanently stopped. The reduced dose of IP will continue to be administered once daily at the same schedule as specified in the Schedule of Assessments (Table 2). The dose of IP may not be increased for the remainder of the study.

Otherwise, IP doses will not be further adjusted for this study except as clinically necessary, eg, interrupting dose due to an AE or serious adverse event (SAE) considered related to IP.

7.5. Criteria for Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to participants, 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 IRB, where required, and initiate withdrawal procedures for participating participants.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

Participants must meet all of the following criteria to qualify for participation in this study:

1. Participant has signed an ICF before any study-specific procedures or washout of drugs is performed.
2. Participant is ambulatory and is 18 to 80 years of age, inclusive, at the time informed consent is obtained.
3. Participant has a diagnosis of ET, as defined by all of the following criteria:
    a. Isolated tremor syndrome consisting of bilateral upper limb action tremor
    b. At least 3 years duration
    c. With or without tremor in other locations (eg, head, voice, or lower limbs)
    d. Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism, isolated focal tremors (eg, voice, head), task- and position-specific tremors, sudden tremor onset or evidence of stepwise deterioration of tremor
4. Participant scores at least 1.5 for each of the six items that comprise the combined total upper limb TETRAS (total performance subscale part 4) with the total score for the dominant upper limb (the sum of the three items for either the right or left upper limb, whichever is dominant) being at least 5.5, at both Screening and predose on Day 1.
5. Participant is willing to discontinue medications taken for the treatment of ET within 14 days or 5 half-lives (whichever is longer) prior to receiving IP. Medications taken for the treatment of ET that were discontinued prior to receiving IP may be resumed following Day 29.
6. Participant is willing to discontinue the use of alcohol and products that contain nicotine within at least 1 week prior to Day 1 and through Day 29 of the study.
7. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does include abstinence).
8. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 13 weeks after receiving study drug, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
9. Male participant is willing to abstain from sperm donation for the duration of the study and for 13 weeks after receiving study drug.
10. Participant has no clinically significant findings, as determined by the investigator, on Screening and predose Day 1 physical examination including mental state examination (MSE) and neurologic examination, 12-lead ECG, or screening clinical laboratory tests.

8.2. Participant Exclusion Criteria

Participants who meet any of the following criteria are disqualified from participation in this study:

1. Participant has presence of known causes of enhanced physiological tremor.
2. Participant has had recent exposure (14 days prior to Day 1) to tremorgenic drugs or presence of alcohol withdrawal state.
3. Participant has had direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor.
4. Participant has had a previous procedure for the treatment of ET, deep brain stimulation, brain lesioning, or magnetic resonance (MR) guided procedure, eg, MR-guided focused ultrasound.
5. Participant has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.)
6. Participant has significant history and/or presence of hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic (hypothyroidism with stable thyroid replacement is acceptable), or oncological disease.
7. Participant has history of substance abuse prior to Screening or has a positive screen for drugs of abuse at Screening or predose on Day 1 or has a positive screen for alcohol predose on Day 1.
8. Participant has a known allergy to SAGE-324 or any excipient.
9. Participant has had exposure to another investigational drug or device within 30 days or 5 half-lives (if known) of the investigational drug, whichever is longer, prior to the Day 1 visit.
10. Participant has history or suicidal behavior within 2 years or answers “YES” to questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk of suicide in the opinion of the investigator.
11. Participant has donated one or more units (1 unit = 450 mL) of blood or experienced acute loss of an equivalent amount of blood within 60 days prior to Day 1.
12. Participant has any condition or comorbidity that in the opinion of the investigator would limit or interfere with the participant’s ability to complete or partake in the study.
13. Participant is unwilling or unable to comply with study procedures and required training.
14. Participant has used any known moderate or strong cytochrome P450 3A4 inhibitors and/or inducers within 14 days or 5 half-lives (whichever is longer) prior to Day 1 or consumed grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St. John’s Wort or products containing these within 30 days prior to Day 1. Use of mild cytochrome inhibitors and/or inducers may be permitted.
15. Participant has concurrent or recent exposure (14 days or 5 half-lives, whichever is longer, prior to the Day 1 visit) to sedative/hypnotic drugs, stimulants, highly caffeinated

beverages or dietary supplements containing high doses of caffeine, or recent increase above regular daily consumption of caffeine.

16. Participant plans to undergo elective surgery or relocate during participation in the study.
17. Participant is investigative site personnel or a member of their immediate families (spouse, parent, child or sibling whether biological or legally adopted).
18. [Removed]
19. Female participant has a positive pregnancy test or confirmed pregnancy.

8.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned IP or entered in the study, ie, a participant who does not meet 1 or more of the eligibility criteria after providing consent and prior to randomization (Day 1). A minimal set of screen failure information will be collected, including demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

8.4. Investigational Product Discontinuation and Early Termination from the Study

8.4.1. Investigational Product Discontinuation

A participant may discontinue IP at any time at his/her own request for any reason. The investigator may discontinue a participant from IP for safety, behavioral, compliance, or administrative reasons. Participants who discontinue IP will be encouraged by the investigator to remain on study and complete the EOT visit, the safety phone call 7 days later, and then, after a further 7 days, the End of Study/Early Termination visit (EOS/ETV), as specified in the Schedule of Assessments (Table 2). If the participant withdraws consent to collect protected health information, the EOS/ETV will be conducted.

The reason for IP discontinuation must be documented in the participant's study record and recorded in the participant's electronic case report form (eCRF).

The investigator must notify the sponsor and/or the medical monitor when a participant stops IP for any reason.

Participants who discontinue IP due to an AE, regardless of investigator-determined causality, should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant.

8.4.2. Early Termination from the Study

A participant may withdraw from the study at any time at his/her own request for any reason. The investigator may discontinue a participant from the study for safety, behavioral, compliance, or administrative reasons.

The reason for early termination from the study must be documented in the participant's study record and recorded in the participant's electronic case report form (eCRF).

The investigator must notify the sponsor and/or the medical monitor when a participant stops participation in the study for any reason.

If a participant is persistently noncompliant, the investigator should discuss with the sponsor the potential discontinuation of the participant. Any reasons for unwillingness or inability to adhere to the protocol must be recorded in the participant's eCRF, including:

- missed visits;
- interruptions in the schedule of study drug administration;
- non-permitted medications

If the participant withdraws from the study after completing 28 days of dosing with IP, they will be encouraged to attend follow-up visits for safety assessments at Day 35 and Day 42, as specified in the Schedule of Assessments (Table 2). If the participant withdraws their consent to collect protected health information, the EOS/ETV visit will be conducted and the participant will be permanently discontinued from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor will retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

8.4.3. Loss to Follow-up

A participant will be deemed lost to follow-up after 3 attempts at contacting the participant have been unsuccessful.

8.4.4. Replacement of Participants

Participants will not be replaced.

9. TREATMENT OF PARTICIPANTS

9.1. Description of Investigational Product

SAGE-324 is an orally administered tablet provided in 5 mg or 15 mg (when available) dose strengths. Participants will receive IP (60 mg total dose of SAGE-324 tablets, or appearance-matched placebo tablets) according to the randomization schedule. Additional details regarding IP preparation, formulation, and storage are included in Section 10.

9.2. Prior Medications, Concomitant Medications, Restrictions, and Contraception Requirements

9.2.1. Prior and Concomitant Medications and/or Supplements

The start and end dates, route, dose/units, frequency, and indication for all medications and/or supplements taken within 30 days prior to signing the informed consent through the first dose of IP will be recorded.

All medications and/or supplements taken from the first dose of IP through the Day 42 (±1 days) visit (including start and end dates route, dose/units, frequency, and indication) will be recorded on the eCRF. Any concomitant medication determined necessary for the welfare of the participant may be given at the discretion of the investigator at any time during the study.

9.2.2. Prohibited Medications

Use or consumption of the following is prohibited for the timeframes specified:

- Treatment with an investigational drug or device during the 30 days or 5 half-lives (if known) of the investigational drug, whichever is longer, prior to Day 1 or during the study.
- Use of tremorgenic drugs within the 14 days or 5 half-lives (whichever is longer) of Day 1 or during the study.
- Use of agents known to affect SAGE-324 drug metabolism (any known cytochrome P450 3A4 inhibitors and/or inducers) within the 14 days or 5 half-lives (whichever is longer) of Day 1 and through Day 29 of the study period. Use of mild cytochrome P inhibitors and/or inducers may be permitted.
- Concomitant use of sedative/hypnotic drugs for 14 days or 5 half-lives prior to Day 1 and during the 28-day dosing period.

9.2.3. Other Restrictions

- Use of any drugs of abuse during the study period is prohibited. Note: participants with a history of drug abuse prior to screening should not be enrolled in the study.
- Use of alcohol within 1 week prior to Day 1 and through Day 29 of the study period is prohibited. If the alcohol test is positive on Days 1, 8, 15, 22, or 29, the participant will not be administered further IP and will be withdrawn from the study; no further efficacy assessments such as TETRAS will be undertaken.

- Use of products that contain nicotine within 1 week prior to Day 1 and through Day 29 of the study period is prohibited. Positive cotinine testing on Days 1, 8, 15, 22, or 29 would be considered a major protocol deviation and the participant will be excluded from the Per Protocol Analysis Set.
- Consumption of grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St. John's Wort or products containing these within 30 days prior to Day 1 and through Day 29 of the study period is prohibited.
- Use of stimulants, highly caffeinated beverages or dietary supplements containing high doses of caffeine within 14 days prior to the Day 1 visit and through Day 29 of the study period is prohibited. Note: participants should not increase their regular daily consumption of caffeine during the study period.

9.2.4. Acceptable Forms of Contraception

Acceptable forms of highly effective contraception for participants of childbearing potential or for partners of male participants who are of childbearing potential include:

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal ligation or bilateral tubal occlusion (performed at least 3 months prior to Screening)
- Vasectomized partner (performed at least 3 months prior to Screening)
- Sexual abstinence (no sexual intercourse)

Acceptable forms of contraception for male participants include:

- Sexual abstinence (no sexual intercourse)
- History of vasectomy (performed at least 3 months prior to Screening)
- Condom with spermicide used together with highly effective female contraceptive methods if the female partner(s) is of childbearing potential (see above for list of acceptable female contraceptive methods)

9.3. Intervention after the End of the Study

There is no planned intervention following the end of the study.

9.4. Treatment Adherence

The first dose of IP will be received and administered by participants in the clinic. Participants will be dispensed a 7-day supply of IP to orally self-administer at home with instructions

specifying to administer in the morning with food. Treatment adherence will be monitored by the site staff at each in-clinic visit by direct questioning and counting returned tablets and will be documented. Details on drug accountability are included in Section 10.6.

Patients will be asked to record the dates and times of their IP dose administrations at home in a diary. They will also record details around how well they complied with the study instructions for self-administering IP at home.

9.5. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Participants will be randomized in a 1:1 ratio to treatment groups (SAGE-324, 60 mg or placebo). Participants, site staff, and the sponsor will be blinded to treatment allocation. Randomization schedules will be generated by an independent statistician. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

9.5.1. Emergency Unblinding

During the study, the blind is to be broken only when the safety of a participant is at risk and the treatment plan is dependent on the study treatment received. Unless a participant is at immediate risk, the investigator should make diligent attempts to contact Sage prior to unblinding the study treatment administered to a participant. Requests from the investigator about the treatment administered to study participants should be discussed with the Sage Medical Monitor. If the unblinding occurs without Sage's knowledge, the investigator must notify Sage within 24 hours of breaking the blind. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

In all cases where the IP allocation for a participant is unblinded, pertinent information (including the reason for unblinding) must be documented in the participant's records and on the eCRF.

If a participant or any study personnel become unblinded to treatment, the participant will be excluded from the Per Protocol analysis set, as detailed further in the statistical analysis plan.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

Table 3: Investigational Product

	Investigational Product	
Product Name:	SAGE-324	Placebo
Dosage Form:	Tablet	Tablet
Tablet Strength	5 mg, 15 mg	0 mg, appearance-matched to 5 mg, and 15 mg, respectively
Route of Administration	Oral	Oral
Physical Description	Immediate release white to off-white, round, film-coated tablet containing 5 mg or 15 mg of SAGE-324 drug substance, and composed of lactose, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and fumed silica, featuring Opadry® II white as the coating agent.	White to off-white, round, film-coated tablet containing no drug substance, composed of lactose, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and fumed silica, featuring Opadry® II white as the coating agent.
Manufacturer	Sage Therapeutics, Inc.	

10.2. Investigational Product Packaging and Labeling

SAGE-324 Oral Tablets and Placebo Tablets will be packaged in blinded, high density polyethylene (HDPE) containers. The containers used for SAGE-324 and placebo will be identical in appearance. The package labeling conforms to FDA and GMP requirements.

10.3. Investigational Product Storage

Upon receipt of the IP, the investigator, or the responsible pharmacist or designee, will inspect the product and acknowledge receipt in accordance with the study-specific process.

The IP must be carefully stored at the temperature specified in the investigator's brochure, securely and separately from other drugs. The IP may not be used for any purpose other than the present study. Any unused IP must be returned per the sponsor's instructions or destroyed locally per the site's procedure(s). IP may not be destroyed until accountability and reconciliation procedures have been completed and monitored.

The investigator or designee will be responsible for ensuring appropriate storage, dispensing, inventory, and accountability of the IP. An accurate, timely record of the disposition of the IP must be maintained.

10.4. Investigational Product Preparation

The IP will be in tablet form and provided in blinded packaging. No preparation is required for the tablet, which is administered orally as described below.

10.5. Investigational Product Administration

The IP will be administered in the clinic or at home as specified in the Schedule of Assessments (Table 2). The IP will be provided as tablets, sufficient in number to achieve a dose of 60 mg. IP will be orally administered once daily in the morning, with food. Participants will be instructed to take the IP with food that comprises a minimum of 400 calories, and to take the IP at approximately the same time each morning.

10.6. Investigational Product Accountability, Handling, and Disposal

Upon receipt of IP, the investigator(s), or the responsible pharmacist or designee, will inspect the IP and complete and follow the instructions regarding receipt and storage in the investigator's brochure and (where applicable) in the Pharmacy Manual. A copy of the shipping documentation will be kept in the study files.

The designated site staff will dispense the supplied participant-specific kits to participants at the planned dispensation visit intervals outlined in the Schedule of Assessments (Table 2).

An interactive response technology (IRT) will be used to capture participant-identifying information. The IRT will be used to randomize the eligible participant into the study and provides the kit number of the IP to be dispensed to that participant.

If dispensing errors or discrepancies are discovered by site staff or sponsor's designee, the sponsor must be notified immediately.

The IP provided is for use only as directed in this protocol. The investigator or designee must keep a record of all IP received, used and returned/discarded.

Sage Therapeutics will be permitted access to the study supplies at any time with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

The investigator, pharmacist, or qualified designee is responsible for drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

At the end of the study, any unused IP tablets will be returned to Sage Therapeutics for destruction or destroyed locally per the site's procedures; disposition of IP will be documented. IP may not be destroyed until accountability and reconciliation procedures have been completed and monitored.

10.7. Product Complaints

A product complaint is any written, electronic, or verbal expression of dissatisfaction regarding the identity, quality, reliability, safety, purity, potency, effectiveness or performance (applicable for approved marketed products) of a drug product after it is released for distribution.

In the course of conduct of the study, study personnel may become aware of a product complaint associated with the use of a Sage product. Personnel shall notify Sage within 24 hours by

forwarding the product complaint information via the contact information listed in Table 1 and in the Pharmacy Manual. Where possible, personnel should segregate and retain any product, materials, or packaging associated with the product complaint until further instruction is provided by Sage or its designated representative(s).

11. EFFICACY ASSESSMENTS AND CLINICAL PHARMACOLOGY ASSESSMENTS

11.1. Efficacy Assessments

11.1.1. The Essential Tremor Rating Assessment Scale

TETRAS is a validated, comprehensive clinical assessment of essential tremor (Elble 2013).

Three different components of TETRAS will be assessed in this study. The TETRAS ADL subscale, total performance score, and performance subscale part 4 upper limb tremor score will each be separately assessed at each clinic visit as specified in the Schedule of Assessments (Table 2).

The ADL subscale assesses how ET is impacting typical activities of daily living (ie, speech, eating, drinking, dressing, personal hygiene, writing, occupational impairment, social impact, and activities affected by upper limb tremor). It consists of 12 items that are each rated on a scale from 0 (normal activity) to 4 (severe abnormality). The overall ADL score range is 0 to 48.

The total performance score is based on overall rating of tremor amplitude in the voice, limbs, head, face, trunk, while performing pre-specified tasks, and also measures functional task capabilities, ie, handwriting, spirography, and holding a pen over a dot. Each of these items is rated on a scale from 0 (no tremor) to 4 (severe tremor). Collectively, the performance items generate an overall performance score from 0 to 64.

For the performance subscale part 4 upper limb tremor score, all 3 maneuvers in the upper limb assessments of part 4 (subscale items 4a, 4b, and 4c) will be completed for both arms, first for the right arm and then for the left. The part 4 subscale ordinally rates postural (limbs extended forward maneuver, and wing-beating [elbows flexed] maneuver), and kinetic (finger-nose-finger maneuver) tremor on a 0 to 4 severity scale in 0.5-point increments.

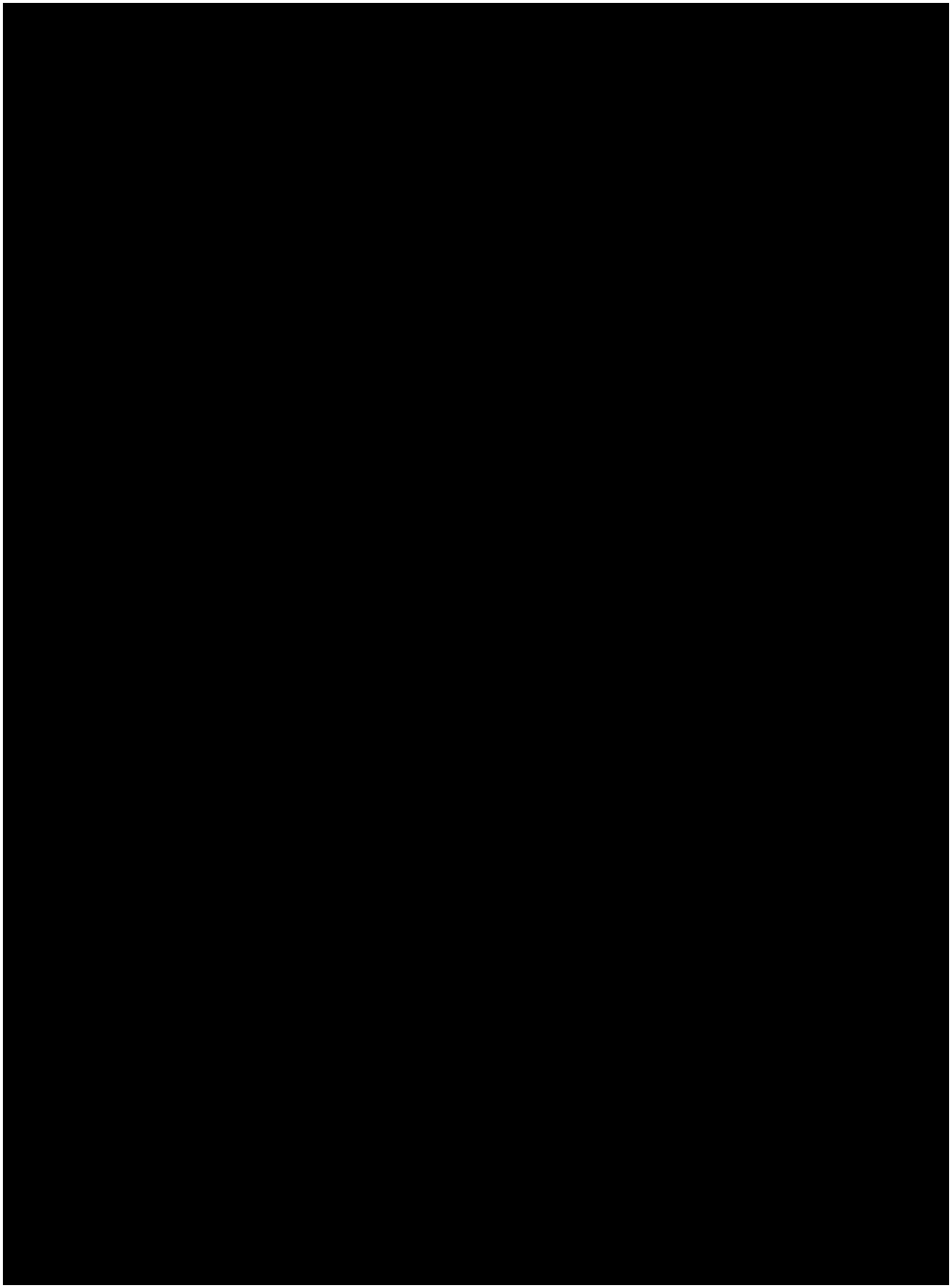
In this study, a videographer will videotape each TETRAS administration.

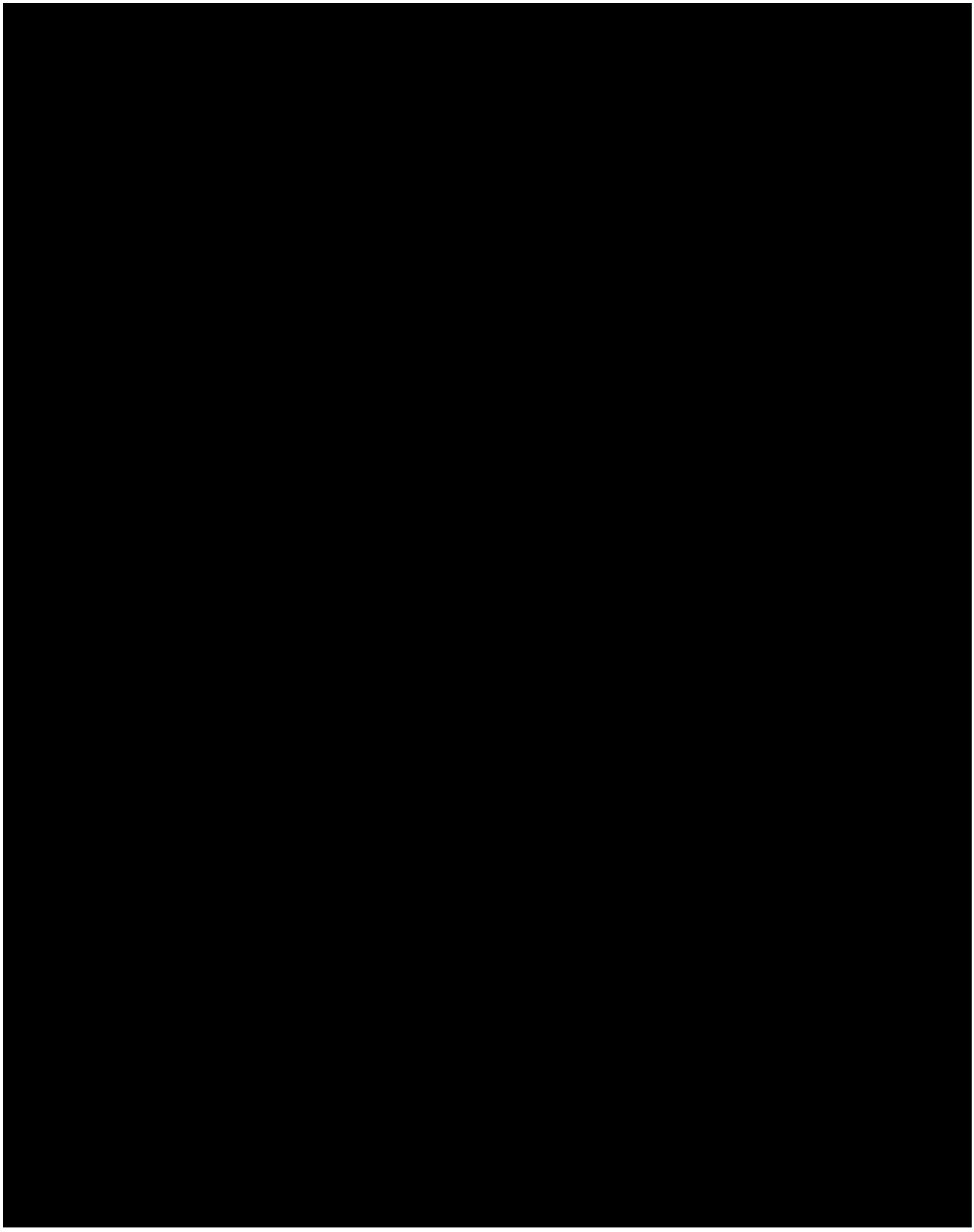
11.1.2. Kinesia ONE™ Accelerometer Score

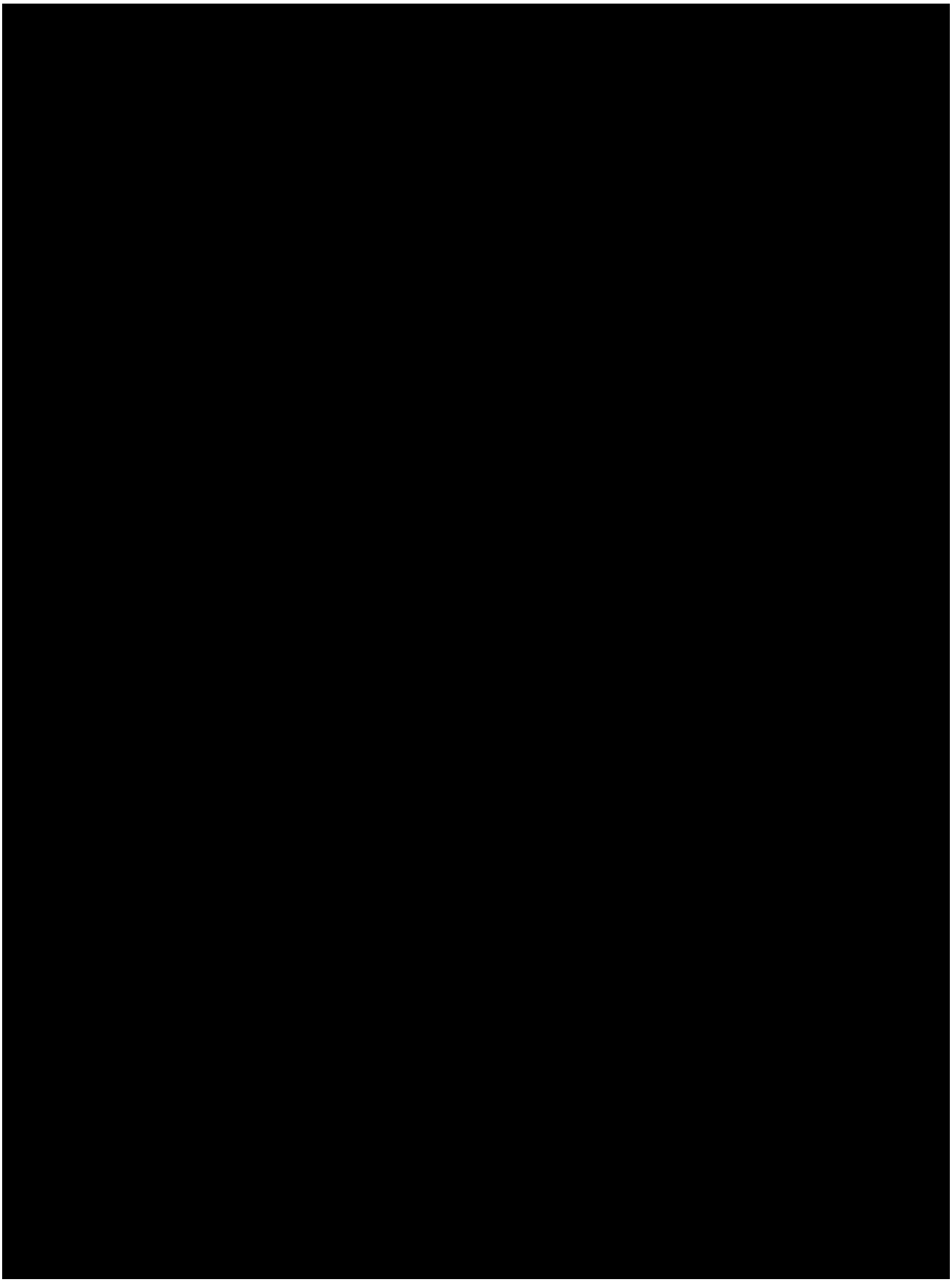
Kinesia ONE™ is an ISO-certified wireless motion sensor worn distally on the index finger, which utilizes 3 orthogonal accelerometers and 3 orthogonal gyroscopes to monitor 3-dimensional motion. Data is transmitted wirelessly from the sensor to a Bluetooth technology-enabled device to use with the Kinesia ONE software (eg, Apple iPad or similar device with preinstalled Kinesia ONE software). The device has received FDA clearance.

Via the Kinesia ONE software application, measures of 3-dimensional motion are converted to scores ranging from 0 to 4, per assessed maneuver; higher scores indicate greater tremor severity. Motion in both arms is captured.

Participants will complete this assessment at each clinic visit as specified in the Schedule of Assessments (Table 2).







[redacted]

11.3. Other Patient-Reported Assessments

11.3.1. Patient Perception of Response Burden

The Patient Perception of Response Burden Questionnaire is a patient-reported measure that assesses the multidimensional construct of response burden (Atkinson 2019).

Participants respond to 6 items assessing 1) how well the questions related to their actual concerns, 2) how comfortable the participants were with answering the questions, 3) how well the survey characterized their health and well-being, 4) the length of time to complete the questionnaires, 5) whether questions seemed unimportant or repetitive, and 6) what additional information should have been gathered. Items 1 to 3 are assessed on a 0 to 10 scale, item 4 is assessed on a 1 to 3 scale, and items 5 and 6 are open-ended. Items 1 and 4 are reverse scored. A composite score can be calculated to create a weighted representative index of relevance, comfort, and well-being relative to time to completion (ie, items 1, 2, and 3 were summed and multiplied by item 4) for a range of 0 to 72, with higher scores indicative of elevated endorsed response burden. The open-ended items will be summarized thematically. The Patient Perception of Response Burden Questionnaire will be performed as specified in the Schedule of Assessments (Table 2).

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

All assessments will be conducted according to the Schedule of Assessments (Table 2).

12.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, ethnicity) and a full medical history will be documented. Whether the participant is left-handed or right-handed will be recorded. This must also additionally include participant recall of history of ET, disease duration, past treatments used, and responsiveness to alcohol and/or other treatments with use intended as off-label treatment of ET (eg, primidone or similar therapies).

12.1.2. Weight and Height

Height and weight will be measured and documented. Body mass index (BMI) will be calculated and documented.

12.1.3. Physical Examination

Whenever possible, the same individual should perform all physical examinations. Physical examinations will include review of systems (eg, head, eye, ear, nose and throat; heart; lungs; abdomen; and extremities) as well as comprehensive neurological examination and MSE. Unscheduled physical examinations may also be conducted per the Investigator's discretion.

Any abnormality in physical examinations will be interpreted by an investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents.

12.1.4. Vital Signs

Vital signs comprise blood pressure and heart rate (supine and standing), respiratory rate, and temperature. Systolic and diastolic blood pressure and heart rate are to be measured after the participant has been supine for at least 5 minutes and then repeated 1 minute and 3 minutes after standing.

Vital signs are measured once at each timepoint with the exception of predose on Day 1, when blood pressure and heart rate are measured supine and standing in triplicate at least 15 minutes apart.

Any abnormality in vital signs will be interpreted by an Investigator as abnormal, NCS; or abnormal, CS in source documents.

12.1.5. Electrocardiogram

A 12-lead ECG will be performed. The standard intervals (heart rate, PR, QRS, QT, and QTcF) as well as any rhythm abnormalities will be recorded.

Electrocardiograms will be performed after the participant has been resting in a supine position for at least 5 minutes. When ECG measurements coincide with safety assessments, vital signs assessment or blood draws, procedures should be carried out in said order (vital signs, ECG, blood draw).

All abnormal ECGs will be interpreted by an investigator as abnormal, NCS, or abnormal, CS in source documents.

12.1.6. Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected. Analytes to be evaluated are summarized in Table 4.

Table 4: Summary of Clinical Laboratory Analytes

Biochemistry	*Renal Panel*: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate *Hepatic Panel*: albumin, ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, total protein, lactate dehydrogenase, gamma glutamyl transferase *Other*: triglycerides, cholesterol (low density lipoprotein [LDL], high density lipoprotein [HDL]), creatine phosphokinase, thyroid stimulating hormone (TSH)
Coagulation	activated partial thromboplastin time, prothrombin time, and international normalized ratio
Hematology	red blood cell count, hemoglobin, hematocrit, white blood cell count with differential, platelet count, and if red blood count indices are abnormal, reflex red blood cell morphology as indicated
Urinalysis	protein, glucose, pH, blood, leukocyte esterase, urobilinogen, bilirubin, ketones, nitrite

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, NCS; or abnormal, CS in source documents.

Follicle stimulating hormone testing will be conducted to confirm whether a participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal (Section 8.1).

12.1.6.1. Drugs of Abuse, Alcohol, Nicotine (Cotinine)

A urine sample will be collected for assessment of the following selected drugs of abuse per the Schedule of Assessments (Table 2): amphetamines, barbiturates, benzodiazepines, cannabinoids/THC, cocaine, methadone, MDMA, methamphetamines, opiates, oxycodone, tricyclic antidepressants, and PCP.

Urine samples will be collected and tested for cotinine. Either urine dipstick or breathalyzer will be used for alcohol testing.

12.1.6.2. Pregnancy Screen

A serum pregnancy test will be conducted for all female participants at Screening; subsequently, a urine pregnancy test will be conducted for all participants of childbearing potential as specified in the Schedule of Assessments (Table 2).

[redacted]

12.1.9. Safety Phone Call

A phone call will be conducted once per week, preferably mid-week in between clinic visits (as specified in Table 2), and again at Day 35, to collect information about current health status, general well-being, IP compliance, or to gather other pertinent health-related information as per investigator judgement.

12.2. Adverse Events and Serious Adverse Events

12.2.1. Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

A TEAE is defined as an AE with onset after the start of IP, or any worsening of a preexisting medical condition/AE with onset after the start of IP and throughout the study. The term IP includes any Sage IP, a comparator, or a placebo administered in a clinical trial.

Laboratory abnormalities [redacted] are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to

be clinically significant. Any abnormalities that meet the criteria for an SAE should be reported in an expedited manner. Laboratory abnormalities [redacted] that are clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

All AEs that occur after any participant has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be reported to Sage Therapeutics.

Participants who discontinue the IP due to an AE, regardless of investigator-determined causality, should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant. Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The sponsor or its representative retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.2. Serious Adverse Event (SAE) Definition

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Places the participant at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

An SAE may also be any other medically important event that, in the opinion of the Investigator may jeopardize the participant or may require medical intervention to prevent 1 of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

All SAEs that occur after any participant has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE report form provided by Sage Therapeutics. Any SAE that is ongoing when the participant completes their final study visit, will be followed by the investigator until the event has resolved, stabilized, returned to baseline status, or until the participant dies or is lost to follow up.

A prescheduled or elective procedure or routinely scheduled treatment will not be considered an SAE, even if the participant is hospitalized. The site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or on a waiting list to be scheduled) prior to obtaining the participant's consent to participate in the study.

- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress, in the opinion of an Investigator, between the participant's consent to participate in the study and at the time of the procedure or treatment.

12.2.3. Definition of Adverse Events of Special Interest

There are no known adverse events of special interest as of the date of signature approval of this clinical protocol.

12.2.4. Relationship to Investigational Product

The investigator must make the determination of relationship to the IP for each AE (not related, related). The following definitions should be considered when evaluating the relationship of AEs and SAEs to the IP.

Not Related	An AE will be considered "not related" to the use of the IP if there is not a reasonable possibility that the event has been caused by the IP. Factors pointing towards this assessment include but are not limited to: the lack of temporal relationship between administration of the IP and the event, the presence of biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE
Related	An AE will be considered "related" to the use of the IP if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point towards this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of alternative explanation for the AE

12.2.5. Recording Adverse Events

AEs spontaneously reported by the participant 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. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, outcome and seriousness (if applicable), and whether or not it caused the participant to discontinue the IP or withdraw early from the study.

Intensity will be assessed according to the following scale:

- Mild: symptom(s) barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s)

- Moderate: symptom(s) of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptom(s) may be needed
- Severe: symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with IP; treatment for symptom(s) may be given and/or participant hospitalized

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2.2. An AE of severe intensity may not necessarily be considered serious.

12.2.6. Reporting Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE(s), the study site must notify Sage or designee within 24 hours of the study site staff becoming aware of the SAE(s). The investigator must complete, sign and date the SAE report form, verify the accuracy of the information recorded on the SAE report form with the corresponding source documents, and send a copy to Sage or designee.

Additional follow-up information, if required or available, should all be sent to Sage or designee within 24 hours of receipt on a follow-up SAE report form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

SAEs occurring after the designated follow up time for the study, should be reported to Sage or designee according to the timelines noted above only if the investigator considers the SAE related to IP.

Sage, or designee, is responsible for notifying the relevant regulatory authorities of certain events. It is the principal investigator's responsibility to notify the IRB/EC of all SAEs that occur at his or her site. Investigators will also be notified of all suspected unexpected serious adverse reactions (SUSARs) that occur during the clinical study. Each site is responsible for notifying its IRB of all SUSARs.

In addition, appropriate personnel in Sage Drug Safety and Pharmacovigilance or designee will unblind SUSARs for the purpose of regulatory reporting. Sage or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Sage, or designee, will submit SUSARs to investigators in a blinded fashion.

12.3. Pregnancy

If a participant becomes pregnant after the first administration of IP, pregnancy information must be collected and recorded on the pregnancy form and submitted to the sponsor within 24 hours of learning of the pregnancy. Details will be collected for all pregnancies for which conception was likely to have occurred after the start of IP administration until 5 terminal half-lives following the last administration of IP or until the completion of the study whichever is longer. Any pregnancy occurring in that time frame will be followed until delivery or termination of the pregnancy. The investigator will also attempt to collect pregnancy information on any participant's partner who becomes pregnant after the participant has received the first

administration of IP. After obtaining the necessary signed informed consent from the pregnant partner directly, the investigator will follow the same pregnancy reporting procedures specified for pregnant participants.

The participant or participant's partner will be followed to determine the outcome of the pregnancy. The outcome of all pregnancies (eg, spontaneous abortion, elective abortion, normal birth) must be followed and documented even if the participant was discontinued from the study. The investigator will collect follow-up information on the participant or participant's partner and the neonate, and the information will be forwarded to Sage or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication. Any complication during pregnancy (eg, anemia, infections, preeclampsia) should be reported as an AE/SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death), the investigator should follow the procedures for reporting an SAE.

12.4. Overdose

An overdose is any dose of IP given to a participant or taken by a participant that exceeds the dose described in the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded.

13. STATISTICS

Detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock. Any changes or additions to the SAP following database lock will be described in detail in the clinical study report.

13.1. Data Analysis Sets

The Randomized Set will include all participants who are randomized.

The Safety Set will include all participants administered IP.

The Full Analysis Set will include all randomized participants who received any amount of IP and have a baseline and at least one postbaseline TETRAS performance subscale part 4 upper limb tremor score.

[redacted]

The Per Protocol Set will include all participants in the Full Analysis Set without any major protocol deviations that could affect efficacy. The review of major protocol deviations will be completed, and the decision on whether the deviation affects efficacy will be documented before database unblinding. Note that a positive cotinine test on Days 1, 8, 15, 22 or 29 constitutes a major protocol deviation.

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All participants will be used in the analyses, as per the analysis populations, using all nonmissing data available. No imputation process will be used to estimate missing data.

13.3. General Considerations

All participant data, including those that are derived, that support the tables and figures will be presented in the participant data listings. Some data may be presented only in participant data listing, some may be presented with a corresponding table or figure; these will be indicated in relevant sections below. Participants will be summarized according to treatment received.

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to receipt of IP.

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

13.4. Demographics and Baseline Characteristics

Demographic data, such as age, race, and ethnicity, and baseline characteristics, such as height, weight, and BMI, will be summarized using the Safety Set.

Pregnancy test results and drug screen results will be listed but not summarized.

Medical history will be listed by participant.

13.5. Efficacy Analysis

The estimand for the primary efficacy analysis is the treatment difference between SAGE-324 and placebo in mean change from baseline in clinic-based TETRAS performance subscale part 4 upper limb tremor scores at Day 29 based on the Full Analysis Set. This will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline TETRAS performance subscale part 4 upper limb tremor score, assessment timepoint, and timepoint-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline clinic visits will be included in the model. The main comparison will be between SAGE-324 and placebo at the 29-day timepoint. Model-based point estimates (ie, least squares means, 5% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz compound symmetry or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not UN, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

Similar to those methods described above for the primary endpoint, an MMRM will be used for the analysis of the change from baseline in TETRAS total performance scores, Kinesia ONE accelerometer scores and TETRAS ADL scores.

Other efficacy analyses will be specified in the SAP. In general, data will be analyzed using appropriate descriptive statistics or prespecified statistical methods as applicable; participant listings will be provided for all efficacy data. Participants will be analyzed according to randomized treatment for the purpose of efficacy unless otherwise specified.

Sensitivity analyses will be described in the SAP.

13.6. Safety Analyses

Safety and tolerability of SAGE-324 will be evaluated by AEs, concomitant medication usage, [redacted] Safety data will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Set using treatment received.

13.6.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or higher. A treatment-emergent adverse event (TEAE) is defined as an AE with onset after the first dose of IP. The analysis of AEs will be based on the concept of TEAEs. The incidence of TEAEs will be summarized by System Organ Class (SOC) and preferred term. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to IP.

Any TEAEs leading to discontinuation of treatment or withdrawal from the study and any treatment-emergent SAEs will be summarized.

All AEs and SAEs (including those with onset or worsening before the start of IP) through the end of the study will be listed.

[redacted]

13.6.3. Physical Examinations

The occurrence of a physical examination, including MSE, (yes/no) and the date performed will be listed by participant.

[redacted]

13.6.6. 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 (WHO-DD) September 2015, or later.

All medications taken within 30 days prior to informed consent through the duration of the study will be recorded. In addition, all psychotropic medications taken in the previous 30 days prior to screening will be recorded. Those medications taken prior to the initiation of the start of IP will be denoted “Prior”. Those medications taken prior to the initiation of the IP and continuing beyond the initiation of the IP or those medications started at the same time or after the initiation of the IP will be denoted “Concomitant”.

Medications will be presented according to whether they are “Prior” or “Concomitant” as defined above. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Details of prior and concomitant medications will be listed by participant, start date, and verbatim term.

13.8. Sample Size and Power

The sample size of this study is based on the assumption of a 3 points difference in the change from baseline TETRAS performance subscale part 4 upper limb tremor score between SAGE-324 and placebo with a standard deviation of 3.5 points. Under these assumptions, a sample size of 25 evaluable participants per group would provide 85% power for detecting a placebo-adjusted treatment difference of 3 points in TETRAS performance subscale part 4 upper limb tremor score assuming a 2-sided test at an alpha level of 0.05. By including 2 treatment groups and using a 1:1 randomization, a total of 50 evaluable participants are required. Assuming a nonevaluability rate of 15%, approximately 60 participants will be randomized. Additional participants may be enrolled if the dropout rate is greater than 15%.

13.8.1. Interim and Data Monitoring Committee (DMC) Analyses

13.8.1.1. Interim Analysis

The sponsor may conduct an interim analysis. Detailed descriptions of planned data analyses will be provided in a separate interim statistical analysis plan (SAP), if applicable.

13.8.1.2. DMC Analysis

Not applicable

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Sage Therapeutics will visit the investigational study site per Sage SOPs to:

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

During the study, a monitor from Sage Therapeutics or representative 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 case report forms, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the participant'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 participant (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or EC.

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

14.2. Audits and Inspections

Sage Therapeutics or authorized representatives of Sage Therapeutics, a regulatory authority, or an independent EC or an IRB may visit the site to perform an audit(s) or inspection(s), including source data verification. The purpose of a Sage Therapeutics audit or a regulatory authority 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/ICH GCP guidelines, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency or IRB/EC about an inspection.

14.3. Institutional Review Board or Ethics Committee

The principal investigator must obtain IRB (or EC) approval for the clinical study prior to enrolling a participant. Initial IRB (or EC) approval, and all materials approved by the IRB (or EC) for this study including the participant consent form and recruitment materials must be maintained by the investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practice and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit(s) at the clinical site. Please see Section 14.2 for more details regarding the audit process.

The investigator must have adequate quality control practices to ensure that the study is performed in a manner consistent with the protocol, GCP/ICH GCP guidelines, and applicable regulatory requirements. The investigator is responsible for reviewing all identified protocol deviations. Significant protocol deviations should be reported to the IRB/EC per the IRB/EC's written procedures.

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. When the investigator retains the services of any individual or party to perform trial-related duties and functions, the investigator must ensure the individual or party is qualified to perform trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed, and any data generated.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained, if necessary, to provide clarification.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF, must be given a written and dated approval or favorable opinion by an IRB or EC as appropriate. The investigator must obtain and document approval before he or she can enroll any participant into the study. The IRB or EC must supply to the sponsor a list of the IRB/EC membership and a statement to confirm that the IRB/EC is organized and operates according to GCP and applicable laws and regulations.

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

The principal investigator is also responsible for providing the IRB or EC with reports of any reportable serious adverse drug reactions from any other study conducted with the IP. Sage Therapeutics will provide this information to the principal investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or EC according to local regulations and guidelines. In addition, the principal investigator must inform the IRB/EC and sponsor of any changes significantly affecting the conduct of the trial and/or increasing the risk to participants (eg, violations to the protocol or urgent safety measures taken for participant safety).

16.2. 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 are consistent with ICH and GCP guidelines, as well as all applicable regional or national regulatory requirements.

16.3. Written Informed Consent

Prior to enrolling a trial participant, the investigator(s) will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and allowed time to consider the information provided.

When the participant decides to participate in the trial, the participant (or the participant's, parent or legally authorized representative) must provide signed and dated informed consent. The written consent must be obtained before conducting any study procedures. The investigator must document the consent process in the participant's source records. The investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant or to the participant's parent or legally authorized representative.

Throughout the trial participants should be informed of any changes made to the study and as new safety and or risk information becomes known. The provision of this information will be documented in the participant's source records, and when applicable, an updated ICF will be provided.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Sage Therapeutics or its representative(s) will be allowed to conduct site visits at the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the facility, drug storage area, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

Inspection of the study by a regulatory authority may occur at any time. The investigator must agree to the inspection of study-related records and source documents by the regulatory authority representative(s).

17.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for the period outlined in the site contract, or for a period of 2 years after the last marketing application approval, and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Sage is responsible to inform the investigator/institution as to when study documents no longer need to be retained.

18. PUBLICATION POLICY

All information concerning SAGE-324 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.

19. LIST OF REFERENCES

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A PHASE 2, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY EVALUATING THE EFFICACY, SAFETY, AND TOLERABILITY OF SAGE-324 IN THE TREATMENT OF INDIVIDUALS WITH ESSENTIAL TREMOR

324-ETD-201

Investigational Product	SAGE-324 Oral Tablet
Clinical Phase	Phase 2
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted] Phone: [redacted] e-mail: [redacted]
Sponsor Medical Monitor	[redacted], MD, PhD
Date of Original Protocol	23 October 2019
Date of Amendment 1	20 December 2019
Date of Amendment 2	24 February 2020
Date of Amendment 3	10 June 2020
Date of Amendment 4	17 December 2020

SPONSOR APPROVAL

Protocol Number:	324-ETD-201
Study Title:	A Phase 2, Double-Blind, Placebo-Controlled, Randomized Study Evaluating the Efficacy, Safety, and Tolerability of SAGE-324 in the Treatment of Individuals with Essential Tremor
Protocol Version and Date:	Version 5, 17 December 2020

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 18-Dec-2020 | 13:32 EST
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Signing Reason: I approve this document
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[redacted], PhD
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Certificate Of Completion

Envelope Id: F888EA4C1D594EE289C033D8C6E572C6
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Subject: SAGE-ETD-201 Amendment 4 signature page v2.pdf
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Document Pages: 2
Signatures: 7
Envelope Originator:
Certificate Pages: 3
Initials: 0
[redacted]
AutoNav: Enabled
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[redacted] [redacted] Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: A0AAC4E8-8B4D-436C-A211-8E0AC6DEBB1E Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 17-Dec-2020 | 14:08 Viewed: 17-Dec-2020 | 14:19 Signed: 17-Dec-2020 | 14:19
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] [redacted] Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: C7339842-D808-4FEE-A2FA-C94300087BC1 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 17-Dec-2020 | 14:08 Viewed: 17-Dec-2020 | 15:18 Signed: 17-Dec-2020 | 15:19
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[redacted] [redacted] [redacted] Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 4CCDE548-C3CA-4F12-AE60-B15F6F5900AE Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 17-Dec-2020 | 14:08 Resent: 18-Dec-2020 | 12:04 Viewed: 18-Dec-2020 | 12:07 Signed: 18-Dec-2020 | 12:07

CONTACT INFORMATION

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Sage Study Physician	[redacted], MD	Phone [redacted]
Sage Medical Monitor	[redacted], MD, PhD	Mobile: [redacted] Office phone: [redacted] E-mail: [redacted]
CRO Medical Monitor and 24-Hour Emergency Contact	[redacted], MD, MPH	[redacted] Phone: [redacted] E-mail: [redacted]
SAE Reporting Information	IQVIA Lifecycle Safety	4820 Emperor Boulevard Durham, NC 27703 E-mail: Sage.Safety@iqvia.com Fax: +1-855-638-1674 SAE Hotline: +1-855-564-2229
Product Complaints	Sage Therapeutics, Inc.	E-mail: productcomplaints@sagerx.com Phone: +1-833-554-7243

2. SYNOPSIS

Name of Sponsor/Company:
Sage Therapeutics, Inc. (hereafter referred to as Sage Therapeutics, or Sage)

Name of Investigational Product:
SAGE-324 Oral Tablet

Name of Active Ingredient:
SAGE-324

Title of Study:
A Phase 2, Double-blind, Placebo-controlled, Randomized Study Evaluating the Efficacy, Safety, and Tolerability of SAGE-324 in the Treatment of Individuals with Essential Tremor

Number of Sites and Study Location: This study will take place at approximately 30 sites in the United States.

Phase of Development: Phase 2

Planned Duration for each Study Participant:
The duration of participation (from Screening through the final follow-up visit) for each participant is estimated to be up to 71 days.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the effect of SAGE-324 compared to placebo on upper limb tremor reduction in individuals with essential tremor (ET) after 28 days of treatment	• Change from baseline compared to placebo in The Essential Tremor Rating Assessment (TETRAS) performance subscale part 4 upper limb tremor score on Day 29
Secondary	
To assess the effect of SAGE-324 compared to placebo on overall upper limb tremor reduction	• Change from baseline compared to placebo in TETRAS performance subscale part 4 upper limb tremor score at all other timepoints • Change from baseline compared to placebo in Kinesia ONE accelerometer scores
To assess the effect of SAGE-324 compared to placebo on activities of daily living (ADLs)	• Change from baseline compared to placebo in TETRAS Scale ADL score
To assess the effect of SAGE-324 compared to placebo on overall tremor	• Change from baseline compared to placebo in TETRAS total performance score
To evaluate the safety and tolerability of SAGE-324	• Incidence of treatment-emergent adverse events (TEAEs)
[redacted]	

[redacted]

Study Description:

This is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of SAGE-324 in individuals with ET. Participants, site staff, and sponsor personnel will be masked to treatment allocation.

This study includes a Screening Period of up to 28 days, a 29-day treatment period (28 days of dosing), and a 14-day follow up period. After providing informed consent, participants will undergo screening assessments as outlined in Table 2 to determine eligibility.

Screening Period: The Screening Period begins with the signing of the informed consent form (ICF). Eligible participants will visit the study center on Day 1 and complete additional eligibility and baseline assessments, as specified in the Schedule of Assessments (Table 2). Following completion of screening and Day 1 eligibility checks, participants will be randomized to 1 of 2 treatment groups (SAGE-324 60 mg daily, or placebo) in a 1:1 ratio.

Double-Blind Treatment Period: Starting on Day 1, participants will receive a single dose of investigational product (IP) once daily for 28 days on an outpatient basis, to be taken in the morning with food that comprises a minimum of 400 calories. Doses occurring on scheduled clinic visits will be administered in the clinic, and doses occurring on all other days will be self-administered by the participant at home. During the Treatment Period, participants will return to the study center approximately once per week for efficacy and safety assessments as specified in Table 2. Participants

will be trained on the use of software applications and devices necessary to complete questionnaires or other assessments. If on Day 1 or at any point during the treatment period participants experience moderate or severe AEs of somnolence, drowsiness, dizziness or similar, or have these events at any severity with associated symptoms such as confusion or balance impairment, they must have a dose interruption (drug holiday) of at least 1 day (missing at least 1 dose). Following a drug holiday, the dose of study drug must then be reduced by 15 mg decrements to tolerability (ie, from 60 mg to 45 mg to 30 mg). The dose of IP may not be increased for the remainder of the study. At the investigator's discretion, participants unable to tolerate the 30 mg dose may be discontinued from study drug. During the study, a phone call will be conducted at least once per week, preferably midway between clinic visits, or as deemed appropriate by the investigator, to review the current status of the participant.

Follow-Up Period: Follow-up visits will be conducted on an outpatient basis. Participants will continue to complete questionnaires as indicated in Table 2 and will receive a phone call approximately 7 days after the last dose of IP (ie, Day 35) for safety monitoring. Participants will return to the study center for an end of study (EOS) visit approximately 14 days following the last dose of IP (ie, Day 42).

Number of Participants (planned): Approximately 60 participants, with approximately 30 per arm.

Eligibility Criteria:

Inclusion Criteria:

1. Participant has signed an ICF before any study-specific procedures or washout of drugs is performed.
2. Participant is ambulatory and is 18 to 80 years of age, inclusive, at the time informed consent is obtained.
3. Participant has a diagnosis of ET, as defined by all of the following criteria:
   a. Isolated tremor syndrome consisting of bilateral upper limb action tremor
   b. At least 3 years duration
   c. With or without tremor in other locations (eg, head, voice, or lower limbs)
   d. Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism, isolated focal tremors (eg, voice, head), task- and position-specific tremors, sudden tremor onset or evidence of stepwise deterioration of tremor
4. Participant scores at least 1.5 for each of the six items that comprise the combined total upper limb TETRAS (total performance subscale part 4) with the total score for the dominant upper limb (the sum of the 3 items for either the right or left upper limb, whichever is dominant) being at least 5.5, at both Screening and predose on Day 1.
5. Participant is willing to completely downtitrate and discontinue from medications taken for the treatment of ET at least 14 days or 5 half-lives (whichever is longer) prior to receiving IP. Medications taken for the treatment of ET that were discontinued prior to receiving IP may be resumed following Day 29.
6. Participant is willing to discontinue the use of alcohol and products that contain nicotine within at least 1 week prior to Day 1 and through Day 29 of the study.
7. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral

salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does include abstinence).

8. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 13 weeks after receiving study drug, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
9. Male participant is willing to abstain from sperm donation for the duration of the study and for 13 weeks after receiving study drug.
10. Participant has no clinically significant findings, as determined by the investigator, on Screening and predose Day 1 physical examination including mental state examination (MSE) and neurologic examination, 12-lead ECG, or screening clinical laboratory tests.

Exclusion Criteria:

1. Participant has presence of known causes of enhanced physiological tremor.
2. Participant has had recent exposure (14 days prior to Day 1) to tremorgenic drugs or presence of alcohol withdrawal state.
3. Participant has had direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor.
4. Participant has had a previous procedure for the treatment of ET, deep brain stimulation, brain lesioning, or magnetic resonance (MR) guided procedure, eg, MR-guided focused ultrasound.
5. Participant has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.)
6. Participant has currently active, medically significant hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic (hypothyroidism with stable thyroid replacement is acceptable), or oncological disease.
7. Participant has history of substance abuse prior to Screening, has a positive screen for drugs of abuse at Screening or predose on Day 1, or has a positive screen for alcohol or cotinine predose on Day 1.
8. Participant has a known allergy to SAGE-324 or any excipient.
9. Participant has had exposure to another investigational drug or device within 30 days or 5 half-lives (if known) of the investigational drug, whichever is longer, prior to the Day 1 visit.
10. Participant has history of suicidal behavior within 2 years or answers “YES” to questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk of suicide in the opinion of the investigator.
11. Participant has donated one or more units (1 unit = 450 mL) of blood or experienced acute loss of an equivalent amount of blood within 60 days prior to Day 1.
12. Participant has any condition or comorbidity that in the opinion of the investigator would limit or interfere with the participant’s ability to complete or partake in the study.
13. Participant is unwilling or unable to comply with study procedures and required training.

14. Participant has used any known moderate or strong cytochrome P450 3A4 inhibitors and/or inducers within 14 days or 5 half-lives (whichever is longer) prior to Day 1 or consumed grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St. John's Wort or products containing these within 30 days prior to Day 1. Use of mild cytochrome inhibitors and/or inducers may be permitted.
15. Participant has concurrent or recent exposure (14 days or five half-lives, whichever is longer, prior to the Day 1 visit) to sedative/hypnotic drugs, stimulants, highly caffeinated beverages or dietary supplements containing high doses of caffeine, or recent increase above regular daily consumption of caffeine.
16. Participant plans to undergo elective surgery or relocate during participation in the study.
17. Participant is investigative site personnel or a member of their immediate families (spouse, parent, child or sibling whether biological or legally adopted).
18. [Removed]
19. Female participant has a positive pregnancy test or confirmed pregnancy.

Investigational Product Dosage and Mode of Administration:

SAGE-324 (60 mg) or matched placebo oral tablets will be administered in the clinic or self-administered once daily, in the morning, at approximately the same time each day, with food that comprises a minimum of 400 calories.

Duration of Treatment:

Each participant will receive a single dose of SAGE-324 oral tablets or matching placebo administered once daily for 28 days.

Statistical Methods:

A separate statistical analysis plan (SAP) will provide a detailed description of the data analyses to be performed in the study. The SAP will be finalized and approved prior to database lock.

General Considerations

For the purpose of all efficacy and safety analyses where applicable, baseline is defined as the last measurement prior to the start of IP administration.

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

Analysis Sets

The Randomized Set is defined as all participants who are randomized.

The Safety Set will include all participants who were administered IP.

The Full Analysis Set will include all randomized participants who received any amount of IP and have a baseline and at least one postbaseline TETRAS performance subscale part 4 upper limb tremor score.

[redacted]

The Per Protocol Set will include all participants in the Full Analysis Set without any major protocol deviations that could affect efficacy. The review of major protocol deviations will be completed, and the decision on whether the deviation affects efficacy will be documented before database unblinding.

Determination of Sample Size

The sample size of this study is based on the assumption of a 3-point difference in the change from baseline TETRAS performance subscale part 4 upper limb tremor scores between SAGE-324 and placebo with a standard deviation of 3.5 points. Under these assumptions, a sample size of 25 evaluable participants per group would provide 85% power for detecting a placebo-adjusted treatment difference of 3 points in TETRAS performance subscale part 4 upper limb tremor score, assuming a 2-sided test at an alpha level of 0.05. By including 2 treatment groups and using a 1:1 randomization, a total of 50 evaluable participants are required. Assuming a nonevaluability rate of 15%, approximately 60 participants will be randomized. Additional participants may be enrolled if the drop-out rate is higher than 15%.

Analysis of Primary Efficacy Endpoint

The estimand for the primary efficacy analysis is the treatment difference between SAGE-324 and placebo in mean change from baseline in clinic-based TETRAS performance subscale part 4 upper limb tremor score at Day 29 based on the Full Analysis Set. This will be analyzed using a mixed-effects model for repeated measures (MMRM); the model will include treatment, baseline TETRAS performance subscale part 4 upper limb tremor score, assessment timepoint, and timepoint-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline clinic visits will be included in the model. The main comparison will be between SAGE-324 and placebo at the 29-day timepoint. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz compound symmetry or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not unstructured, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

Analysis of Secondary Efficacy Endpoints

Similar to those methods described above for the primary endpoint, an MMRM will be used to analyze of the change from baseline in TETRAS total performance scores, Kinesia ONE accelerometer scores and TETRAS ADL scores. Individual items of the TETRAS subscales will be summarized.

Safety Analysis

Safety and tolerability of study drug will be evaluated by incidence of TEAEs/serious adverse events,

[redacted]

Interim Analysis

The sponsor may conduct an interim analysis. Detailed descriptions of planned data analyses will be provided in a separate interim statistical analysis plan (SAP), if applicable.

Table 2: Schedule of Assessments

Assessment	Screening	Treatment Period									Follow-up Period	
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15(±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**35 (±1) Safety Phone Call**	**42 (±1) EOS/ETV**
Informed Consent	X											
Inclusion/Exclusion	X	X										
Demographics	X											
Medical History	X											
Pregnancy Test	X (serum; all women)	X (urine; WOCBP only)				X (urine; WOCBP only)				X (urine; WOCBP only)		X (urine; WOCBP only)
FSH (postmenopausal women only)	X											
Randomization[a]		X										
Alcohol/cotinine screens		X		X		X		X		X		
Drug screen	X	X										
Physical examination[b]	X	X		X		X		X		X		X
Neurological examination including MSE[b]	X	X		X		X		X		X		X
Body height	X											
Body weight	X											
Vital signs[c]	X	X		X		X		X		X		X
12-Lead ECG[d]	X	X		X		X		X		X		X
Chemistry/hematology/ coagulation/urinalysis	X	X		X		X		X		X		X

Assessment	Screening	Treatment Period									Follow-up Period	
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15(±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**35 (±1) Safety Phone Call**	**42 (±1) EOS/ETV**
[redacted]												
Kinesia ONE[f]	X	X		X		X		X		X		X
TETRAS[g]	X	X		X		X		X		X		X
[redacted]												

Assessment	Screening	Treatment Period									Follow-up Period	
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15(±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**35 (±1) Safety Phone Call**	**42 (±1) EOS/ETV**
Patient Perception of Response Burden										X		X
[redacted]												
Participant training[h]	X	X										
Dispense study drug		X		X		X		X				
IP administration [i]		Administered once daily for 28 days							Not applicable			
AEs/SAEs	X											
Prior and concomitant medication and history[j]	X											

Abbreviations: ADL = activities of daily living; AE = adverse event; [redacted]; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; [redacted]; ETV = early termination visit; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; ICF = informed consent form; min = minutes; IP = investigational product; MSE = mental state examination; [redacted]; SAE = serious adverse event; TETRAS = The Essential Tremor Rating Assessment Scale; WOCBP = women of childbearing potential

Notes:

- The suggested order of assessments during clinic visits is: vital signs, TETRAS, Kinesia ONE, ECG, blood sample collection for [redacted] and clinical laboratory assessments, and questionnaires.
- All assessments will be performed predose unless specified in a footnote.

[a] Randomization will occur on Day 1 after meeting all eligibility criteria.

[b] Complete physical examinations (including MSE and comprehensive neurologic examination) should be performed as specified and additionally as clinically necessary (see Section 12.1.3).

[c] Predose on Day 1, supine and standing blood pressure and heart rate will be collected in triplicate at least 15 minutes apart, measured after the participant has been in the supine position for at least 5 minutes and then repeated 1 minute and 3 minutes after standing. Respiratory rate and temperature are collected once predose on Day 1. Vital signs will be collected once predose at all other visits. All postdose vital signs will be collected once at approximately 3 hours (±60 min) after dosing.

[d] ECGs will be collected and read centrally. ECGs will be performed predose and approximately 3 hours (±60 min) postdose. All ECGs must be performed after the participant has been in a supine position for at least 5 minutes.

[redacted]

[f] Kinesia ONE will be assessed subsequently to TETRAS Performance subscale part 4 upper limb tremor.

[g] The TETRAS Performance and TETRAS ADL subscales will be assessed at Screening and predose at each clinic visit. The TETRAS Performance subscale part 4 upper limb tremor will be assessed before Kinesia ONE. In addition, on Day 15, the TETRAS Performance subscale will be assessed at 5 and 8 hours (±30 min) postdose. A videographer will record each TETRAS administration.

[h] Participants will be trained by study personnel on the use of software applications, Investigational Product Diary, and devices necessary for the conduct of the study.

[i] On Day 1, participants will receive the first dose of IP at the research site and will be observed for AEs before leaving the site. A phone call to follow up on any AE(s) will be conducted, if deemed appropriate by the investigator, to review the current status of the participant.

[j] Prior medications will be recorded during Screening and will include all medications and supplements taken within the 30 days prior to signing the ICF through the first dose of IP, as well as a complete history of all treatments for ET since the year of diagnosis. Concomitant medications will be recorded thereafter throughout the duration of the study.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ADL	activities of daily living
ADR	adverse drug reaction
AUC_{inf}	area under the curve from 0 to infinity
$AUC_{0\text{-}tau}$	area under the concentration-time curve from 0 to end of the dosing period
BMI	body mass index
[redacted]	[redacted]
C_{max}	maximum observed concentration
CRO	contract research organization
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End-of-Study
[redacted]	[redacted]
[redacted]	[redacted]
ET	essential tremor
[redacted]	[redacted]
ETV	early termination visit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
PD	pharmacodynamic
[redacted]	[redacted]
PI	principal investigator

Abbreviation	Definition
PK	pharmacokinetic
[redacted]	
PV	Pharmacovigilance
QTcF	QT corrected according to Fridericia's formula
[redacted]	
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
t_{max}	time of occurrence of C_{max}
WHO	World Health Organization

5. INTRODUCTION

SAGE-324 is a positive allosteric modulator (PAM) of A-type γ-aminobutyric acid-gated chloride channel ($GABA_A$) receptors, the major class of inhibitory neurotransmitter receptors in the brain. In addition to being developed as an adjunctive therapy in epilepsy and other seizure disorders under IND 139201, SAGE-324 is also being developed for the treatment of Essential Tremor (ET).

Essential tremor is a permanently debilitating, neurologically determined, common movement disorder characterized by involuntary rhythmic oscillation of a body part due to intermittent muscle contractions typically occurring when not at rest, thus interfering with fine motor skills associated with daily activities (Olanow 2008, Deuschl 2011, Hopfner 2016, NIH 2019). Although the pathophysiology and etiology of ET is not fully understood, it is postulated that approximately 50% of ET patients feature an autosomal dominant pattern of familial inheritance and that non-inherited cases may have toxin-based or other causality (Olanow 2008, Hopfner 2016). ET is the most common movement disorder in the US, with prevalence estimated to be approximately 2.2% of the population, representing a substantial societal medical burden with over an estimated 7 million ET patients in the US alone (Louis 2014).

In general, active tasks of daily life are adversely impacted by ET, including but not limited to speech, handwriting, household tasks, and occupational demands, contributing negatively to psychosocial well-being, general anxiety, and overall quality of life (Koller, 1989). Although benign in term of its effect on life expectancy, ET is a progressive neurodegenerative condition whose symptoms are typically disabling, often forcing patients to change jobs or seek early retirement (Zappia, 2013). In some cases, serious disability may ensue.

The pharmacological profile of SAGE-324 is theorized to induce therapeutic effect in the treatment of ET. Based on preclinical studies of SAGE-324, which features a different mechanism of action than that of propranolol, the pharmacokinetic (PK)/ pharmacodynamic (PD) profile suggests SAGE-324 may safely ameliorate symptoms in patients suffering from ET, regardless of propranolol use.

There are currently ongoing Phase 1 clinical studies of SAGE-324 in healthy adults and in adults with ET. These studies, in addition to preclinical studies of SAGE-324, are detailed in the investigator's brochure.

With a $GABA_A$ receptor-based mechanism of action featuring positive allosteric modulation capability, SAGE-324 represents a novel approach to the treatment of ET, which may help address the unmet medical need of the ET population, warranting further study of SAGE-324 as a potential treatment for this common movement disorder.

Henceforth, this double-blind, placebo-controlled efficacy and safety study of SAGE-324 will be conducted in adults and is designed to assess the effect of SAGE-324 on a variety of outcome measures specific to ET disease characteristics and associated quality of life domains.

5.1. Dose Justification

The dose of SAGE-324 planned for this study is 60 mg given as oral tablets, to be administered once daily in the morning with food. The dose was selected based on preliminary data from 3 active studies of SAGE-324, which included: unblinded data from completed cohorts in

324-CLP-101 Part A (oral solution SAGE-324 doses of 3 mg, 10 mg, 30 mg, 45 mg, 60 mg); Part C (oral solution SAGE-324 doses of 30 mg); Part D (oral suspension SAGE-324 doses of 30 mg) in healthy subjects; and preliminary data from open-label Part E (oral suspension SAGE-324 doses of 45 mg and 60 mg) in participants with ET; additional preliminary data from 324-CLP-102 cohorts 1 through 6 (cohorts 1 to 5 unblinded, cohort 6 blinded), which evaluated oral suspension doses ranging from 5 mg to 60 mg; and preliminary unblinded data from 324-CLP-104, which compared the relative bioavailability of the oral tablet (30 mg) vs oral suspension (30 mg) formulations of SAGE-324 and separately the effect of food on the PK of the SAGE-324 oral tablet. In 324-CLP-101 and 324-CLP-102 studies, doses were administered in a fasted state. The preliminary data from all of these active studies collectively informed the route of administration (oral) and dose strength of 60 mg as oral tablets planned for further evaluation in this study.

SAGE-324 was generally well-tolerated in participants with ET and in healthy volunteers, as was shown in the preliminary data of 324-CLP-101 Part E at single administration doses of 45 mg and 60 mg, and in 324-CLP-102 through once-daily administered doses of up to 60 mg for 14 days. In addition, tremor reduction was observed at both doses on TETRAS and Kinesia ONE accelerometry, with greater improvement seen at 60 mg compared to 45 mg.

In the clinically complete study 324-CLP-104, preliminary data showed that SAGE-324 oral tablets, when coadministered with a meal, resulted in exposures approximately equivalent to that of SAGE-324 oral suspension under fasted conditions. Therefore, the SAGE-324 oral tablets are recommended to be administered with food.

5.2. Benefit/Risk Assessment

Based on the mechanism of action of SAGE-324 and the results of completed nonclinical studies and preliminary data of currently ongoing clinical studies of SAGE-324, it is theorized that participants may have symptomatic amelioration, ie, tremor reduction and possibly improved quality of life from potentially stabilizing disease characteristics associated with ET.

Potential risks anticipated in this study are based on available data from toxicology studies of SAGE-324 in addition to preliminary data from 3 ongoing, currently active Phase 1 clinical studies of SAGE-324.

Available preliminary clinical data are summarized in the SAGE-324 Investigator's Brochure. There have been no deaths or SAEs related to IP, and based on the preliminary clinical data available, there have been no confirmed clinically significant trends in clinical laboratory evaluations, vital signs, or physical examinations.

Based on available preliminary clinical data from SAGE-324 active clinical studies, AEs of somnolence and feeling of relaxation are considered adverse drug reactions (ADRs). In addition to scheduled clinic visits, the current status of study participants will be reviewed via phone calls in between clinic visits, or more frequently for AE monitoring.

6. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To assess the effect of SAGE-324 compared to placebo on upper limb tremor reduction in individuals with essential tremor (ET) after 28 days of treatment	• Change from baseline compared to placebo in The Essential Tremor Rating Assessment (TETRAS) performance subscale part 4 upper limb tremor score on Day 29
Secondary	
To assess the effect of SAGE-324 compared to placebo on overall upper limb tremor reduction	• Change from baseline compared to placebo in TETRAS performance subscale part 4 upper limb tremor score at all other timepoints • Change from baseline compared to placebo in Kinesia ONE accelerometer scores
To assess the effect of SAGE-324 compared to placebo on activities of daily living (ADLs)	• Change from baseline compared to placebo in TETRAS Scale ADL score
To assess the effect of SAGE-324 compared to placebo on overall tremor	• Change from baseline compared to placebo in TETRAS total performance score
To evaluate the safety and tolerability of SAGE-324	• Incidence of treatment-emergent adverse events (TEAEs)

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy, safety, and tolerability of SAGE-324 in individuals with ET. Participants, site staff, and sponsor personnel will be masked to treatment allocation (see Section 9.5).

This study includes a Screening Period of up to 28 days, a 29-day treatment period consisting of 28 days of dosing with the end of treatment visit intended to be on Day 29 at trough, and a 14-day follow-up period relative to final dose (Figure 1). After providing informed consent, participants will undergo screening assessments as outlined in Table 2 to determine eligibility.

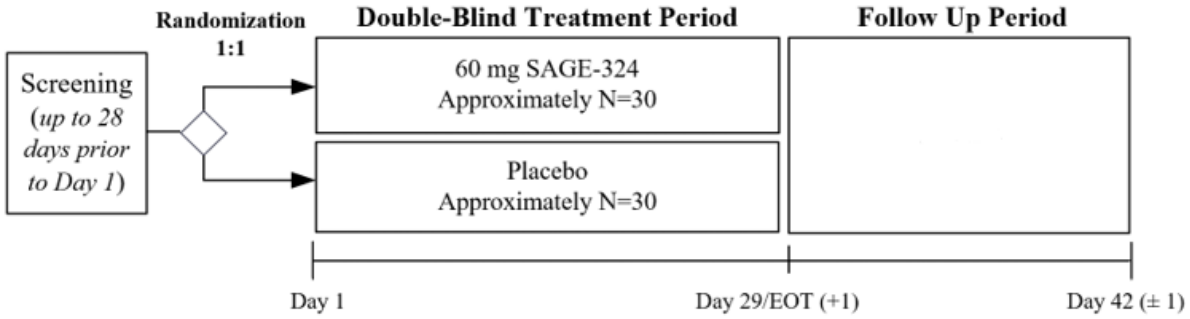
The Screening Period begins with the signing of the informed consent form (ICF). Eligible participants will visit the study center on Day 1 and complete additional eligibility assessments of safety and efficacy, as specified in the Schedule of Assessments (Table 2). Following completion of screening and Day 1 eligibility checks, participants will be randomized to 1 of 2 treatment groups (SAGE-324 60 mg daily, or placebo) in a 1:1 ratio.

During the double-blind Treatment Period, starting on Day 1, participants will receive a single dose of investigational product (IP) once daily in the morning with food for 28 days on an outpatient basis (see Section 10.5). Doses occurring on scheduled clinic visits will be administered in the clinic, and doses occurring on all other days will be self-administered by the participant at home as specified in Table 2. During the Treatment Period, participants will return to the study center approximately once per week for efficacy and safety assessments as specified in Table 2. If on Day 1 or at any point during the treatment period, participants experience moderate or severe AEs of somnolence, drowsiness, dizziness or similar, or experience these events at any severity with associated symptoms such as confusion or balance impairment, they must have a dose interruption (drug holiday) of at least 1 day (missing at least 1 dose). Following a drug holiday, the dose of study drug must then be reduced by 15 mg decrements to tolerability (ie, from 60 mg to 45 mg to 30 mg). The dose of IP may not be increased for the remainder of the study. At the investigator's discretion, participants unable to tolerate the 30-mg dose will be discontinued from IP. During the study, a phone call will be conducted once per week, preferably midway between clinic visits, or more frequently if deemed appropriate by the investigator, to review the current status of the participant. Details regarding dose adjustment criteria and procedures are provided in Section 7.4.

In addition to Kinesia ONE-specific training, clinical study center staff and study participants will be trained on the use of software applications and devices necessary to complete questionnaires or other assessments as required. During in-clinic visits, clinical study center staff will be available to assist participants as needed, to ensure they can access and use the software applications and devices correctly according to the training.

During the follow-up period, visits will be conducted on an outpatient basis. In addition to the phone calls to review current status, participants will receive a phone call approximately 7 days after the last dose of IP (ie, Day 35) for safety monitoring. Participants will return to the study center for an end of study visit approximately 14 days following the last dose of IP (ie, Day 42).

Figure 1: Study Design



Abbreviation: EOT = end of treatment

7.2. Number of Participants

Approximately 60 participants are planned, with approximately 30 participants enrolled per arm, to produce 25 evaluable participants per arm for primary efficacy analysis. Additional participants may be randomized if the drop-out rate is higher than anticipated (ie, >15%).

7.3. Treatment Assignment

Participants will be assigned to IP (active or placebo) in accordance with the randomization schedule on Day 1. Additional details on randomization and blinding are provided in Section 9.5.

7.4. Dose Adjustment Criteria

If a participant reports moderate or severe adverse events (as defined in Section 12.2.5) of somnolence, drowsiness, dizziness, or similar events or experiences these events at any severity with associated symptoms such as confusion or balance impairment on Day 1 or at any point during the treatment period, the participant must have a drug holiday (dose interruption) of at least 1 day (missing at least 1 dose) (Table 2). The drug holiday must be followed by reducing the dose of IP from 60 mg to 45 mg (ie, from 4 tablets of 15 mg to 3 tablets of 15 mg).

If the events persist and continue to be moderate or severe, despite the drug holiday and dose reduction, or the participant experiences a new moderate or severe AE of somnolence, drowsiness, dizziness or similar, the participant must have a further drug holiday of at least 1 day and a further dose reduction from 45 mg to 30 mg (from 3 tablets to 2 tablets).

The participant's condition must be closely monitored via phone calls or in-person visits to assess the impact of any drug holiday and dose reduction.

The reduced dose of IP will continue to be administered once daily at the same schedule as specified in the Schedule of Assessments (Table 2). The dose of IP may not be increased for the remainder of the study.

Following a second drug holiday and dose reduction to 30 mg, if the events persist or recur and are moderate or severe, the investigator must discontinue the participant from the IP. The dose may not be reduced below 30 mg.

The investigator will continue to institute drug holidays, dose reductions, or IP discontinuation over and above this minimum as clinically appropriate.

7.5. Criteria for Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to participants, 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 IRB, where required, and initiate withdrawal procedures for participating participants.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

Participants must meet all of the following criteria to qualify for participation in this study:

1. Participant has signed an ICF before any study-specific procedures or washout of drugs is performed.
2. Participant is ambulatory and is 18 to 80 years of age, inclusive, at the time informed consent is obtained.
3. Participant has a diagnosis of ET, as defined by all of the following criteria:
    a. Isolated tremor syndrome consisting of bilateral upper limb action tremor
    b. At least 3 years duration
    c. With or without tremor in other locations (eg, head, voice, or lower limbs)
    d. Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism, isolated focal tremors (eg, voice, head), task- and position-specific tremors, sudden tremor onset or evidence of stepwise deterioration of tremor
4. Participant scores at least 1.5 for each of the six items that comprise the combined total upper limb TETRAS (total performance subscale part 4) with the total score for the dominant upper limb (the sum of the three items for either the right or left upper limb, whichever is dominant) being at least 5.5, at both Screening and predose on Day 1.
5. Participant is willing to completely downtitrate and discontinue from medications taken for the treatment of ET at least 14 days or 5 half-lives (whichever is longer) prior to receiving IP. Medications taken for the treatment of ET that were discontinued prior to receiving IP may be resumed following Day 29.
6. Participant is willing to discontinue the use of alcohol and products that contain nicotine within at least 1 week prior to Day 1 and through Day 29 of the study.
7. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.4 during participation in the study and for 30 days following the last dose of study drug, unless she is postmenopausal (at least 12 months of spontaneous amenorrhea without an alternative medical cause, with confirmatory follicle stimulating hormone >40 mIU/mL), and/or surgically sterile (bilateral oophorectomy, hysterectomy, and/or bilateral salpingectomy), or does not engage in sexual relations which carry a risk of pregnancy (does include abstinence).
8. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 13 weeks after receiving study drug, unless the participant does not engage in sexual relation(s) which carry a risk of pregnancy. Acceptable methods of effective contraception are listed in Section 9.2.4.
9. Male participant is willing to abstain from sperm donation for the duration of the study and for 13 weeks after receiving study drug.
10. Participant has no clinically significant findings, as determined by the investigator, on Screening and predose Day 1 physical examination including mental state examination (MSE) and neurologic examination, 12-lead ECG, or screening clinical laboratory tests.

8.2. Participant Exclusion Criteria

Participants who meet any of the following criteria are disqualified from participation in this study:

1. Participant has presence of known causes of enhanced physiological tremor.
2. Participant has had recent exposure (14 days prior to Day 1) to tremorgenic drugs or presence of alcohol withdrawal state.
3. Participant has had direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor.
4. Participant has had a previous procedure for the treatment of ET, deep brain stimulation, brain lesioning, or magnetic resonance (MR) guided procedure, eg, MR-guided focused ultrasound.
5. Participant has historical or clinical evidence of tremor with psychogenic origin (including but not limited to eating disorders, major depression, etc.)
6. Participant has currently active, medically significant hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, ophthalmologic, metabolic (hypothyroidism with stable thyroid replacement is acceptable), or oncological disease.
7. Participant has history of substance abuse prior to Screening or has a positive screen for drugs of abuse at Screening or predose on Day 1 or has a positive screen for alcohol or cotinine predose on Day 1.
8. Participant has a known allergy to SAGE-324 or any excipient.
9. Participant has had exposure to another investigational drug or device within 30 days or 5 half-lives (if known) of the investigational drug, whichever is longer, prior to the Day 1 visit.
10. Participant has history or suicidal behavior within 2 years or answers “YES” to questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk of suicide in the opinion of the investigator.
11. Participant has donated one or more units (1 unit = 450 mL) of blood or experienced acute loss of an equivalent amount of blood within 60 days prior to Day 1.
12. Participant has any condition or comorbidity that in the opinion of the investigator would limit or interfere with the participant’s ability to complete or partake in the study.
13. Participant is unwilling or unable to comply with study procedures and required training.
14. Participant has used any known moderate or strong cytochrome P450 3A4 inhibitors and/or inducers within 14 days or 5 half-lives (whichever is longer) prior to Day 1 or consumed grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St. John’s Wort or products containing these within 30 days prior to Day 1. Use of mild cytochrome inhibitors and/or inducers may be permitted.
15. Participant has concurrent or recent exposure (14 days or 5 half-lives, whichever is longer, prior to the Day 1 visit) to sedative/hypnotic drugs, stimulants, highly caffeinated

beverages or dietary supplements containing high doses of caffeine, or recent increase above regular daily consumption of caffeine.

16. Participant plans to undergo elective surgery or relocate during participation in the study.
17. Participant is investigative site personnel or a member of their immediate families (spouse, parent, child or sibling whether biological or legally adopted).
18. [Removed]
19. Female participant has a positive pregnancy test or confirmed pregnancy.

8.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned IP or entered in the study, ie, a participant who does not meet 1 or more of the eligibility criteria after providing consent and prior to randomization (Day 1). A minimal set of screen failure information will be collected, including demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

8.4. Investigational Product Discontinuation and Early Termination from the Study

8.4.1. Investigational Product Discontinuation

A participant may discontinue IP at any time at his/her own request for any reason. The investigator may discontinue a participant from IP for safety, behavioral, compliance, or administrative reasons. Participants who discontinue IP will be encouraged by the investigator to remain on study and complete the EOT visit, the safety phone call 7 days later, and then, after a further 7 days, the End of Study/Early Termination visit (EOS/ETV), as specified in the Schedule of Assessments (Table 2). If the participant withdraws consent to collect protected health information, the EOS/ETV will be conducted.

The reason for IP discontinuation must be documented in the participant's study record and recorded in the participant's electronic case report form (eCRF).

The investigator must notify the sponsor and/or the medical monitor when a participant stops IP for any reason.

Participants who discontinue IP due to an AE, regardless of investigator-determined causality, should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant.

8.4.2. Early Termination from the Study

A participant may withdraw from the study at any time at his/her own request for any reason. The investigator may discontinue a participant from the study for safety, behavioral, compliance, or administrative reasons.

The reason for early termination from the study must be documented in the participant's study record and recorded in the participant's electronic case report form (eCRF).

The investigator must notify the sponsor and/or the medical monitor when a participant stops participation in the study for any reason.

If a participant is persistently noncompliant, the investigator should discuss with the sponsor the potential discontinuation of the participant. Any reasons for unwillingness or inability to adhere to the protocol must be recorded in the participant's eCRF, including:

- missed visits;
- interruptions in the schedule of study drug administration;
- non-permitted medications

If the participant withdraws from the study after completing 28 days of dosing with IP, they will be encouraged to attend follow-up visits for safety assessments at Day 35 and Day 42, as specified in the Schedule of Assessments (Table 2). If the participant withdraws their consent to collect protected health information, the EOS/ETV visit will be conducted and the participant will be permanently discontinued from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor will retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

8.4.3. Loss to Follow-up

A participant will be deemed lost to follow-up after 3 attempts at contacting the participant have been unsuccessful.

8.4.4. Replacement of Participants

Participants will not be replaced. However, additional participants may be enrolled if the drop-out rate is higher than 15%.

9. TREATMENT OF PARTICIPANTS

9.1. Description of Investigational Product

SAGE-324 is an orally administered tablet provided in 15 mg dose strengths. Participants will receive IP (60 mg total dose of SAGE-324 tablets, or appearance-matched placebo tablets) according to the randomization schedule. Additional details regarding IP preparation, formulation, and storage are included in Section 10.

9.2. Prior Medications, Concomitant Medications, Restrictions, and Contraception Requirements

9.2.1. Prior and Concomitant Medications and/or Supplements

The start and end dates, route, dose/units, frequency, and indication for all medications and/or supplements taken within 30 days prior to signing the informed consent through the first dose of IP will be recorded.

All medications and/or supplements taken from the first dose of IP through the Day 42 (±1 days) visit (including start and end dates route, dose/units, frequency, and indication) will be recorded on the eCRF. Any concomitant medication determined necessary for the welfare of the participant may be given at the discretion of the investigator at any time during the study.

9.2.2. Prohibited Medications

Use or consumption of the following is prohibited for the timeframes specified:

- Treatment with an investigational drug or device during the 30 days or 5 half-lives (if known) of the investigational drug, whichever is longer, prior to Day 1 or during the study.
- Use of tremorgenic drugs within the 14 days or 5 half-lives (whichever is longer) of Day 1 or during the study.
- Use of agents known to affect SAGE-324 drug metabolism (any known cytochrome P450 3A4 inhibitors and/or inducers) within the 14 days or 5 half-lives (whichever is longer) of Day 1 and through Day 29 of the study period. Use of mild cytochrome P inhibitors and/or inducers may be permitted.
- Concomitant use of sedative/hypnotic drugs for 14 days or 5 half-lives prior to Day 1 and during the 28-day dosing period.
- Any prior ET medications must be discontinued prior to the Screening TETRAS:
  - There must be 14 days or 5 half-lives (whichever is longer) washout period prior to the Day 1 (baseline) visit.
  - For drugs requiring downtitration, there must be the required number of days for downtitration plus 14 days or 5 half-lives (whichever is longer) prior to the Day 1 (baseline) visit.

9.2.3. Other Restrictions

- Use of any drugs of abuse during the study period is prohibited. Note: participants with a history of drug abuse prior to screening should not be enrolled in the study.
- Use of alcohol within 1 week prior to Day 1 and through Day 29 of the study period is prohibited. If the alcohol test is positive on Days 1, 8, 15, 22, or 29, the participant will not be administered further IP and will be withdrawn from the study; no further efficacy assessments such as TETRAS will be undertaken.
- Use of products that contain nicotine within 1 week prior to Day 1 and through Day 29 of the study period is prohibited. Positive cotinine testing on Days 8, 15, 22, or 29 would be considered a major protocol deviation and the participant will be excluded from the Per Protocol Analysis Set. Positive cotinine testing on Day 1 is exclusionary.
- Consumption of grapefruit juice, grapefruit, Seville oranges, pomegranates, tangelos, or St. John's Wort or products containing these within 30 days prior to Day 1 and through Day 29 of the study period is prohibited.
- Use of stimulants, highly caffeinated beverages or dietary supplements containing high doses of caffeine within 14 days prior to the Day 1 visit and through Day 29 of the study period is prohibited. Note: participants should not increase their regular daily consumption of caffeine during the study period.

9.2.4. Acceptable Forms of Contraception

Acceptable forms of highly effective contraception for participants of childbearing potential or for partners of male participants who are of childbearing potential include:

- Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception associated with inhibition of ovulation
- Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal ligation or bilateral tubal occlusion (performed at least 3 months prior to Screening)
- Vasectomized partner (performed at least 3 months prior to Screening)
- Sexual abstinence (no sexual intercourse)

Acceptable forms of contraception for male participants include:

- Sexual abstinence (no sexual intercourse)
- History of vasectomy (performed at least 3 months prior to Screening)

- Condom with spermicide used together with highly effective female contraceptive methods if the female partner(s) is of childbearing potential (see above for list of acceptable female contraceptive methods)

9.3. Intervention after the End of the Study

There is no planned intervention following the end of the study.

9.4. Treatment Adherence

The first dose of IP will be received and administered by participants in the clinic. Participants will be dispensed a 7-day supply of IP to orally self-administer at home with instructions specifying to administer in the morning with food. Treatment adherence will be monitored by the site staff at each in-clinic visit by direct questioning and counting returned tablets and will be documented. Details on drug accountability are included in Section 10.6.

Patients will be asked to record the dates and times of their IP dose administrations at home in a diary. They will also record details around how well they complied with the study instructions for self-administering IP at home.

9.5. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Participants will be randomized in a 1:1 ratio to treatment groups (SAGE-324, 60 mg or placebo). Participants, site staff, and the sponsor will be blinded to treatment allocation. Randomization schedules will be generated by an independent statistician. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

9.5.1. Emergency Unblinding

During the study, the blind is to be broken only when the safety of a participant is at risk and the treatment plan is dependent on the study treatment received. Unless a participant is at immediate risk, the investigator should make diligent attempts to contact Sage prior to unblinding the study treatment administered to a participant. Requests from the investigator about the treatment administered to study participants should be discussed with the Sage Medical Monitor. If the unblinding occurs without Sage's knowledge, the investigator must notify Sage within 24 hours of breaking the blind. All circumstances surrounding a premature unblinding must be clearly documented in the source records.

In all cases where the IP allocation for a participant is unblinded, pertinent information (including the reason for unblinding) must be documented in the participant's records and on the eCRF.

If a participant or any study personnel become unblinded to treatment, the participant will be excluded from the Per Protocol analysis set, as detailed further in the statistical analysis plan.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

Table 3: Investigational Product

	Investigational Product	
Product Name:	SAGE-324	Placebo
Dosage Form:	Tablet	Tablet
Tablet Strength	15 mg	0 mg, appearance-matched to 15 mg, respectively
Route of Administration	Oral	Oral
Physical Description	Immediate release white to off-white, round, film-coated tablet containing 15 mg of SAGE-324 drug substance, and composed of lactose, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and fumed silica, featuring Opadry® II white as the coating agent.	White to off-white, round, film-coated tablet containing no drug substance, composed of lactose, microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate and fumed silica, featuring Opadry® II white as the coating agent.
Manufacturer	Sage Therapeutics, Inc.	

10.2. Investigational Product Packaging and Labeling

SAGE-324 Oral Tablets and Placebo Tablets will be packaged in blinded, high density polyethylene (HDPE) containers. The containers used for SAGE-324 and placebo will be identical in appearance. The package labeling conforms to FDA and GMP requirements.

10.3. Investigational Product Storage

Upon receipt of the IP, the investigator, or the responsible pharmacist or designee, will inspect the product and acknowledge receipt in accordance with the study-specific process.

The IP must be carefully stored at the temperature specified in the investigator's brochure, securely and separately from other drugs. The IP may not be used for any purpose other than the present study. Any unused IP must be returned per the sponsor's instructions or destroyed locally per the site's procedure(s). IP may not be destroyed until accountability and reconciliation procedures have been completed and monitored.

The investigator or designee will be responsible for ensuring appropriate storage, dispensing, inventory, and accountability of the IP. An accurate, timely record of the disposition of the IP must be maintained.

10.4. Investigational Product Preparation

The IP will be in tablet form and provided in blinded packaging. No preparation is required for the tablet, which is administered orally as described below.

10.5. Investigational Product Administration

The IP will be administered in the clinic or at home as specified in the Schedule of Assessments (Table 2). The IP will be provided as tablets, sufficient in number to achieve a dose of 60 mg. IP will be orally administered once daily in the morning, with food. Participants will be instructed to take the IP with food that comprises a minimum of 400 calories, and to take the IP at approximately the same time each morning.

If a participant reports moderate or severe adverse events (as defined in Section 12.2.5) of somnolence, drowsiness, dizziness, or similar events, or experiences these events at any severity with associated symptoms such as confusion or balance impairment on Day 1 or at any point during the treatment period, the dose must be adjusted per the criteria in Section 7.4.

10.6. Investigational Product Accountability, Handling, and Disposal

Upon receipt of IP, the investigator(s), or the responsible pharmacist or designee, will inspect the IP and complete and follow the instructions regarding receipt and storage in the investigator's brochure and (where applicable) in the Pharmacy Manual. A copy of the shipping documentation will be kept in the study files.

The designated site staff will dispense the supplied participant-specific kits to participants at the planned dispensation visit intervals outlined in the Schedule of Assessments (Table 2).

An interactive response technology (IRT) will be used to capture participant-identifying information. The IRT will be used to randomize the eligible participant into the study and provides the kit number of the IP to be dispensed to that participant.

If dispensing errors or discrepancies are discovered by site staff or sponsor's designee, the sponsor must be notified immediately.

The IP provided is for use only as directed in this protocol. The investigator or designee must keep a record of all IP received, used and returned/discarded.

Sage Therapeutics will be permitted access to the study supplies at any time with appropriate notice during or after completion of the study to perform drug accountability reconciliation.

The investigator, pharmacist, or qualified designee is responsible for drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

At the end of the study, any unused IP tablets will be returned to Sage Therapeutics for destruction or destroyed locally per the site's procedures; disposition of IP will be documented. IP may not be destroyed until accountability and reconciliation procedures have been completed and monitored.

10.7. Product Complaints

A product complaint is any written, electronic, or verbal expression of dissatisfaction regarding the identity, quality, reliability, safety, purity, potency, effectiveness or performance (applicable for approved marketed products) of a drug product after it is released for distribution.

In the course of conduct of the study, study personnel may become aware of a product complaint associated with the use of a Sage product. Personnel shall notify Sage within 24 hours by forwarding the product complaint information via the contact information listed in Table 1 and in the Pharmacy Manual. Where possible, personnel should segregate and retain any product, materials, or packaging associated with the product complaint until further instruction is provided by Sage or its designated representative(s).

11. EFFICACY ASSESSMENTS AND CLINICAL PHARMACOLOGY ASSESSMENTS

11.1. Efficacy Assessments

11.1.1. The Essential Tremor Rating Assessment Scale

TETRAS is a validated, comprehensive clinical assessment of essential tremor (Elble 2013).

Three different components of TETRAS will be assessed in this study. The TETRAS ADL subscale, total performance score, and performance subscale part 4 upper limb tremor score will each be separately assessed at each clinic visit as specified in the Schedule of Assessments (Table 2).

The ADL subscale assesses how ET is impacting typical activities of daily living (ie, speech, eating, drinking, dressing, personal hygiene, writing, occupational impairment, social impact, and activities affected by upper limb tremor). It consists of 12 items that are each rated on a scale from 0 (normal activity) to 4 (severe abnormality). The overall ADL score range is 0 to 48.

The total performance score is based on overall rating of tremor amplitude in the voice, limbs, head, face, trunk, while performing pre-specified tasks, and also measures functional task capabilities, ie, handwriting, spirography, and holding a pen over a dot. Each of these items is rated on a scale from 0 (no tremor) to 4 (severe tremor). Collectively, the performance items generate an overall performance score from 0 to 64.

For the performance subscale part 4 upper limb tremor score, all 3 maneuvers in the upper limb assessments of part 4 (subscale items 4a, 4b, and 4c) will be completed for both arms, first for the right arm and then for the left. The part 4 subscale ordinally rates postural (limbs extended forward maneuver, and wing-beating [elbows flexed] maneuver), and kinetic (finger-nose-finger maneuver) tremor on a 0 to 4 severity scale in 0.5-point increments.

In this study, a videographer will videotape each TETRAS administration.

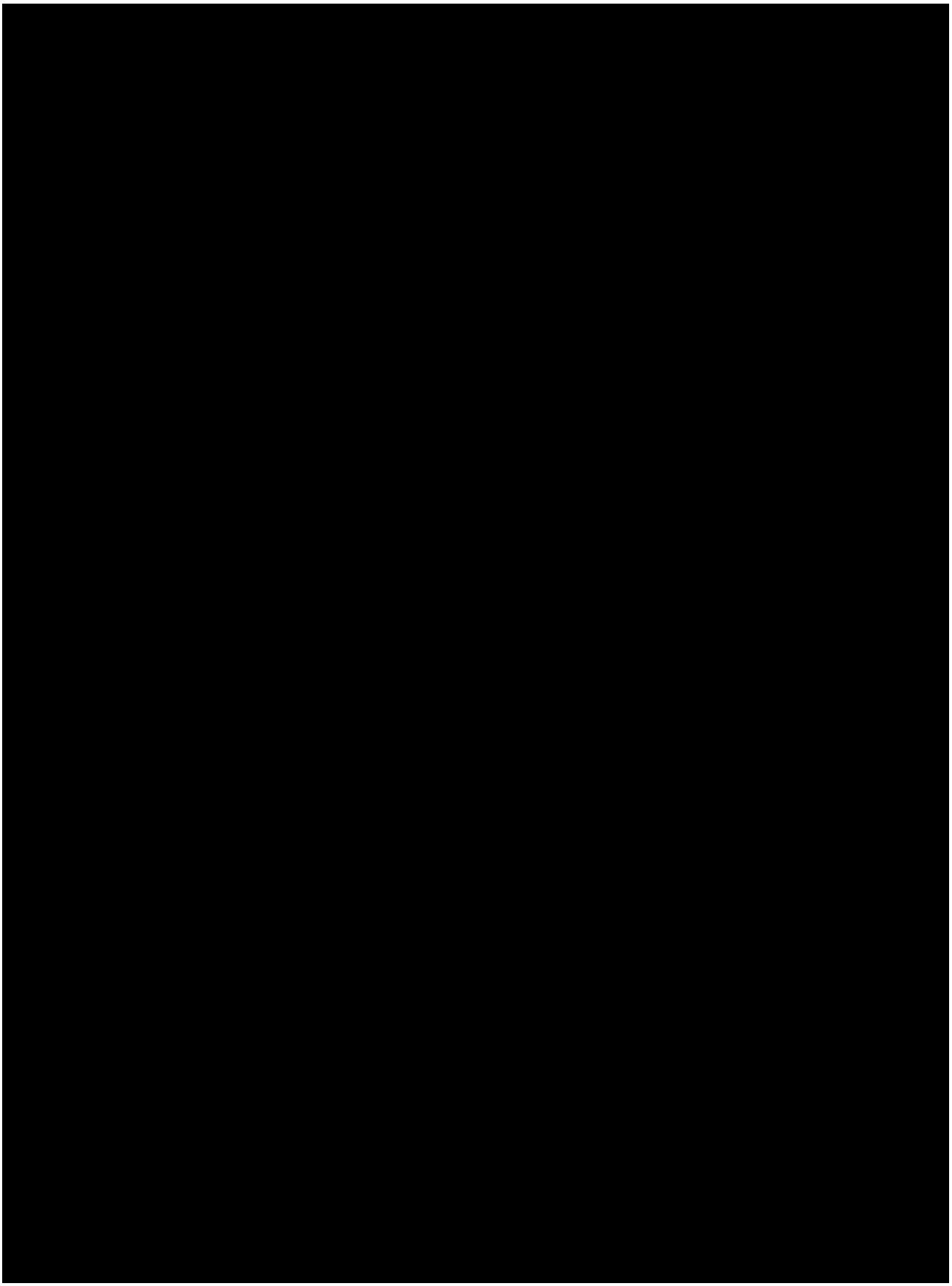
Prior medications for ET must be discontinued prior to Screening TETRAS ratings (see Section 9.2.2 for washout periods).

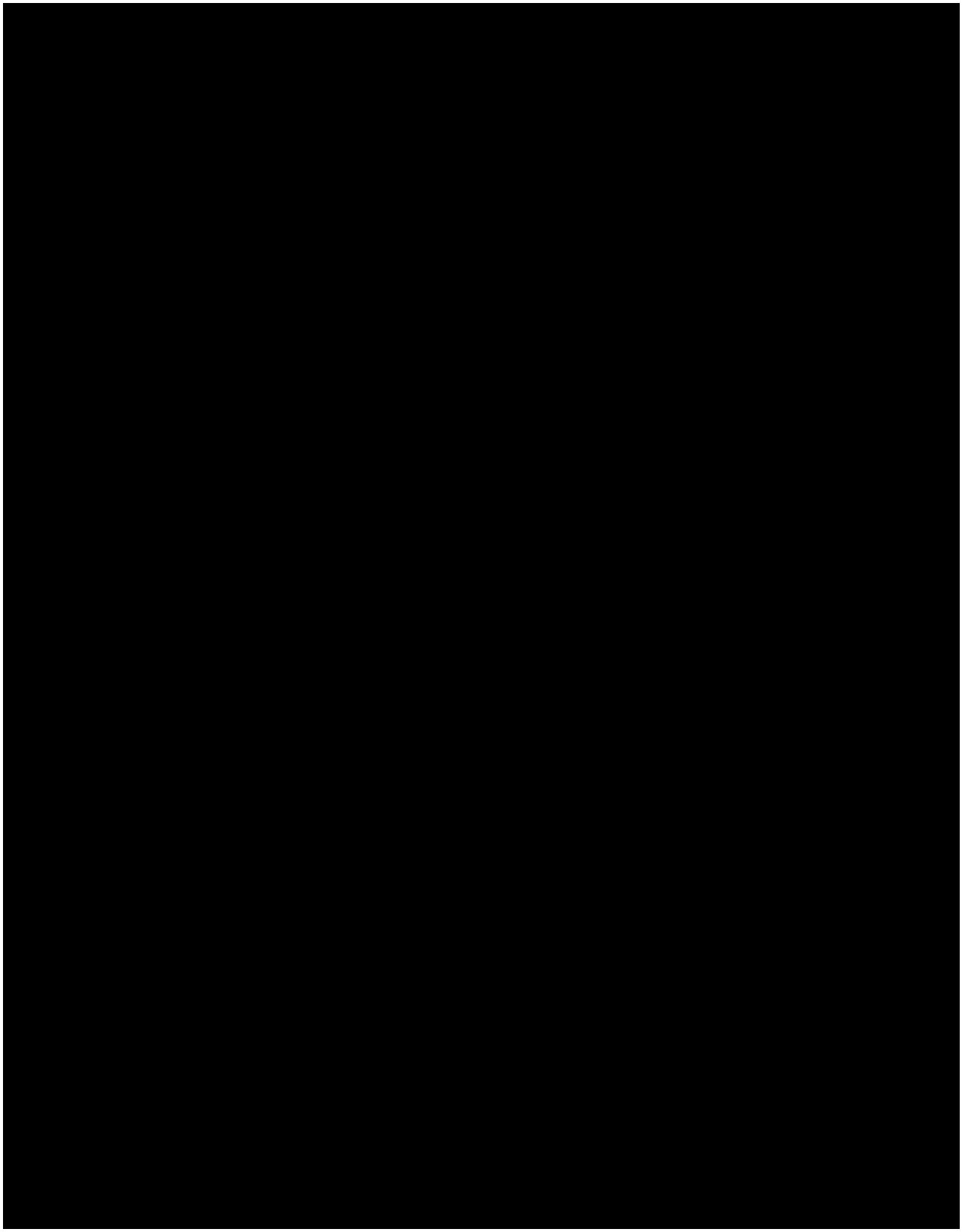
11.1.2. Kinesia ONE™ Accelerometer Score

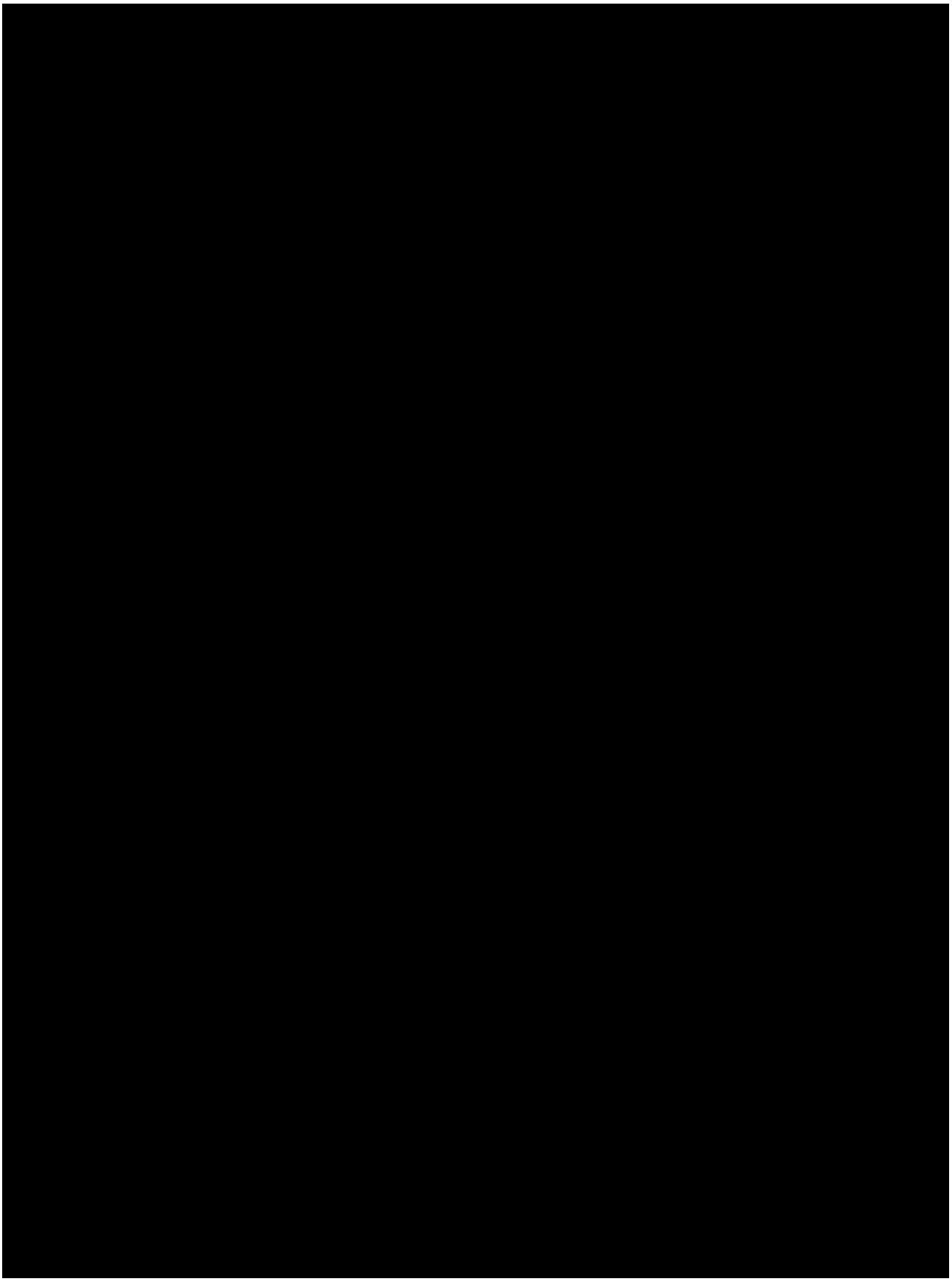
Kinesia ONE™ is an ISO-certified wireless motion sensor worn distally on the index finger, which utilizes 3 orthogonal accelerometers and 3 orthogonal gyroscopes to monitor 3-dimensional motion. Data is transmitted wirelessly from the sensor to a Bluetooth technology-enabled device to use with the Kinesia ONE software (eg, Apple iPad or similar device with preinstalled Kinesia ONE software). The device has received FDA clearance.

Via the Kinesia ONE software application, measures of 3-dimensional motion are converted to scores ranging from 0 to 4, per assessed maneuver; higher scores indicate greater tremor severity. Motion in both arms is captured.

Participants will complete this assessment at each clinic visit as specified in the Schedule of Assessments (Table 2).







[redacted]

11.3. Other Patient-Reported Assessments

11.3.1. Patient Perception of Response Burden

The Patient Perception of Response Burden Questionnaire is a patient-reported measure that assesses the multidimensional construct of response burden (Atkinson 2019).

Participants respond to 6 items assessing 1) how well the questions related to their actual concerns, 2) how comfortable the participants were with answering the questions, 3) how well the survey characterized their health and well-being, 4) the length of time to complete the questionnaires, 5) whether questions seemed unimportant or repetitive, and 6) what additional information should have been gathered. Items 1 to 3 are assessed on a 0 to 10 scale, item 4 is assessed on a 1 to 3 scale, and items 5 and 6 are open-ended. Items 1 and 4 are reverse scored. A composite score can be calculated to create a weighted representative index of relevance, comfort, and well-being relative to time to completion (ie, items 1, 2, and 3 were summed and multiplied by item 4) for a range of 0 to 72, with higher scores indicative of elevated endorsed response burden. The open-ended items will be summarized thematically. The Patient Perception of Response Burden Questionnaire will be performed as specified in the Schedule of Assessments (Table 2).

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

All assessments will be conducted according to the Schedule of Assessments (Table 2).

12.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, ethnicity) and a full medical history will be documented. Whether the participant is left-handed or right-handed will be recorded. This must also additionally include participant recall of history of ET, disease duration, past treatments used, and responsiveness to alcohol and/or other treatments with use intended as off-label treatment of ET (eg, primidone or similar therapies).

12.1.2. Weight and Height

Height and weight will be measured and documented. Body mass index (BMI) will be calculated and documented.

12.1.3. Physical Examination

Whenever possible, the same individual should perform all physical examinations. Physical examinations will include review of systems (eg, head, eye, ear, nose and throat; heart; lungs; abdomen; and extremities) as well as comprehensive neurological examination and MSE. Unscheduled physical examinations may also be conducted per the Investigator's discretion.

Any abnormality in physical examinations will be interpreted by an investigator as abnormal, not clinically significant (NCS); or abnormal, clinically significant (CS) in source documents.

12.1.4. Vital Signs

Vital signs comprise blood pressure and heart rate (supine and standing), respiratory rate, and temperature. Systolic and diastolic blood pressure and heart rate are to be measured after the participant has been supine for at least 5 minutes and then repeated 1 minute and 3 minutes after standing.

Vital signs are measured once at each timepoint with the exception of predose on Day 1, when blood pressure and heart rate are measured supine and standing in triplicate at least 15 minutes apart.

Any abnormality in vital signs will be interpreted by an Investigator as abnormal, NCS; or abnormal, CS in source documents.

12.1.5. Electrocardiogram

A 12-lead ECG will be performed. The standard intervals (heart rate, PR, QRS, QT, and QTcF) as well as any rhythm abnormalities will be recorded.

Electrocardiograms will be performed after the participant has been resting in a supine position for at least 5 minutes. When ECG measurements coincide with safety assessments, vital signs assessment or blood draws, procedures should be carried out in said order (vital signs, ECG, blood draw).

All abnormal ECGs will be interpreted by an investigator as abnormal, NCS, or abnormal, CS in source documents.

12.1.6. Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected. Analytes to be evaluated are summarized in Table 4.

Table 4: Summary of Clinical Laboratory Analytes

Biochemistry	*Renal Panel*: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate *Hepatic Panel*: albumin, ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, total protein, lactate dehydrogenase, gamma glutamyl transferase *Other*: triglycerides, cholesterol (low density lipoprotein [LDL], high density lipoprotein [HDL]), creatine phosphokinase, thyroid stimulating hormone (TSH)
Coagulation	activated partial thromboplastin time, prothrombin time, and international normalized ratio
Hematology	red blood cell count, hemoglobin, hematocrit, white blood cell count with differential, platelet count, and if red blood count indices are abnormal, reflex red blood cell morphology as indicated
Urinalysis	protein, glucose, pH, blood, leukocyte esterase, urobilinogen, bilirubin, ketones, nitrite

All clinical laboratory test results outside the reference range will be interpreted by the Investigator as abnormal, NCS; or abnormal, CS in source documents.

Follicle stimulating hormone testing will be conducted to confirm whether a participant with ≥12 months of spontaneous amenorrhea meets the protocol-defined criteria for being postmenopausal (Section 8.1).

12.1.6.1. Drugs of Abuse, Alcohol, Nicotine (Cotinine)

A urine sample will be collected for assessment of the following selected drugs of abuse per the Schedule of Assessments (Table 2): amphetamines, barbiturates, benzodiazepines, cannabinoids/THC, cocaine, methadone, MDMA, methamphetamines, opiates, oxycodone, tricyclic antidepressants, and PCP.

Urine samples will be collected and tested for cotinine. Either urine dipstick or breathalyzer will be used for alcohol testing.

12.1.6.2. Pregnancy Screen

A serum pregnancy test will be conducted for all female participants at Screening; subsequently, a urine pregnancy test will be conducted for all participants of childbearing potential as specified in the Schedule of Assessments (Table 2).

[redacted]

12.1.9. Safety Phone Call

A phone call will be conducted once per week, preferably mid-week in between clinic visits (as specified in Table 2), and again at Day 35, to collect information about current health status, general well-being, IP compliance, or to gather other pertinent health-related information as per investigator judgement.

If a dose interruption (drug holiday) followed by a dose reduction is required, the investigator will speak with the participant to provide instructions via the phone or the participant will have an in-person visit.

12.2. Adverse Events and Serious Adverse Events

12.2.1. Adverse Event Definition

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

A TEAE is defined as an AE with onset after the start of IP, or any worsening of a preexisting medical condition/AE with onset after the start of IP and throughout the study. The term IP includes any Sage IP, a comparator, or a placebo administered in a clinical trial.

Laboratory abnormalities [redacted] are considered AEs if they result in discontinuation or interruption of study treatment, require therapeutic medical intervention, meet protocol specific criteria (if applicable) or if the investigator considers them to be clinically significant. Any abnormalities that meet the criteria for an SAE should be reported in an expedited manner. Laboratory abnormalities [redacted] that are clearly attributable to another AE do not require discrete reporting (eg, electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis).

All AEs that occur after any participant has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be reported to Sage Therapeutics.

Participants who discontinue the IP due to an AE, regardless of investigator-determined causality, should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant. Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The sponsor or its representative retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.2. Serious Adverse Event (SAE) Definition

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Places the participant at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect

An SAE may also be any other medically important event that, in the opinion of the Investigator may jeopardize the participant or may require medical intervention to prevent 1 of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization).

All SAEs that occur after any participant has signed the ICF and throughout the duration of the study, whether or not they are related to the study, must be recorded on the SAE report form provided by Sage Therapeutics. Any SAE that is ongoing when the participant completes their final study visit, will be followed by the investigator until the event has resolved, stabilized, returned to baseline status, or until the participant dies or is lost to follow up.

A prescheduled or elective procedure or routinely scheduled treatment will not be considered an SAE, even if the participant is hospitalized. The site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or on a waiting list to be scheduled) prior to obtaining the participant's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress, in the opinion of an Investigator, between the participant's consent to participate in the study and at the time of the procedure or treatment.

12.2.3. Definition of Adverse Events of Special Interest

There are no known adverse events of special interest as of the date of signature approval of this clinical protocol.

12.2.4. Relationship to Investigational Product

The investigator must make the determination of relationship to the IP for each AE (not related, related). The following definitions should be considered when evaluating the relationship of AEs and SAEs to the IP.

Not Related	An AE will be considered "not related" to the use of the IP if there is not a reasonable possibility that the event has been caused by the IP. Factors pointing towards this assessment include but are not limited to: the lack of temporal relationship between administration of the IP and the event, the presence of biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE
Related	An AE will be considered "related" to the use of the IP if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point towards this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE, or a lack of alternative explanation for the AE

12.2.5. Recording Adverse Events

AEs spontaneously reported by the participant 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. The AE term should be reported in standard medical terminology when possible. For each AE, the investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, outcome and seriousness (if applicable), and whether or not it caused the participant to discontinue the IP or withdraw early from the study.

Intensity will be assessed according to the following scale:

- Mild: symptom(s) barely noticeable to participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s)
- Moderate: symptom(s) of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptom(s) may be needed
- Severe: symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with IP; treatment for symptom(s) may be given and/or participant hospitalized

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2.2. An AE of severe intensity may not necessarily be considered serious.

12.2.6. Reporting Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE(s), the study site must notify Sage or designee within 24 hours of the study site staff becoming aware of the SAE(s). The investigator must complete, sign and date the SAE report form, verify the accuracy of the information recorded on the SAE report form with the corresponding source documents, and send a copy to Sage or designee.

Additional follow-up information, if required or available, should all be sent to Sage or designee within 24 hours of receipt on a follow-up SAE report form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

SAEs occurring after the designated follow up time for the study, should be reported to Sage or designee according to the timelines noted above only if the investigator considers the SAE related to IP.

Sage, or designee, is responsible for notifying the relevant regulatory authorities of certain events. It is the principal investigator's responsibility to notify the IRB/EC of all SAEs that occur at his or her site. Investigators will also be notified of all suspected unexpected serious adverse reactions (SUSARs) that occur during the clinical study. Each site is responsible for notifying its IRB of all SUSARs.

In addition, appropriate personnel in Sage Drug Safety and Pharmacovigilance or designee will unblind SUSARs for the purpose of regulatory reporting. Sage or designee will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Sage, or designee, will submit SUSARs to investigators in a blinded fashion.

12.3. Pregnancy

If a participant becomes pregnant after the first administration of IP, pregnancy information must be collected and recorded on the pregnancy form and submitted to the sponsor within 24 hours of learning of the pregnancy. Details will be collected for all pregnancies for which conception was likely to have occurred after the start of IP administration until 5 terminal half-lives following the last administration of IP or until the completion of the study whichever is longer. Any

pregnancy occurring in that time frame will be followed until delivery or termination of the pregnancy. The investigator will also attempt to collect pregnancy information on any participant's partner who becomes pregnant after the participant has received the first administration of IP. After obtaining the necessary signed informed consent from the pregnant partner directly, the investigator will follow the same pregnancy reporting procedures specified for pregnant participants.

The participant or participant's partner will be followed to determine the outcome of the pregnancy. The outcome of all pregnancies (eg, spontaneous abortion, elective abortion, normal birth) must be followed and documented even if the participant was discontinued from the study. The investigator will collect follow-up information on the participant or participant's partner and the neonate, and the information will be forwarded to Sage or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication. Any complication during pregnancy (eg, anemia, infections, preeclampsia) should be reported as an AE/SAE. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death), the investigator should follow the procedures for reporting an SAE.

12.4. Overdose

An overdose is any dose of IP given to a participant or taken by a participant that exceeds the dose described in the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on an overdose form and sent to Sage or designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded.

13. STATISTICS

Detailed description of the analyses to be performed in the study will be provided in the statistical analysis plan (SAP). The SAP will be finalized and approved prior to database lock. Any changes or additions to the SAP following database lock will be described in detail in the clinical study report.

13.1. Data Analysis Sets

The Randomized Set will include all participants who are randomized.

The Safety Set will include all participants administered IP.

The Full Analysis Set will include all randomized participants who received any amount of IP and have a baseline and at least one postbaseline TETRAS performance subscale part 4 upper limb tremor score.

[redacted]

The Per Protocol Set will include all participants in the Full Analysis Set without any major protocol deviations that could affect efficacy. The review of major protocol deviations will be completed, and the decision on whether the deviation affects efficacy will be documented before database unblinding. Note that a positive cotinine test on Days 1, 8, 15, 22 or 29 constitutes a major protocol deviation.

13.2. Handling of Missing Data

Every attempt will be made to avoid missing data. All participants will be used in the analyses, as per the analysis populations, using all nonmissing data available. No imputation process will be used to estimate missing data.

13.3. General Considerations

All participant data, including those that are derived, that support the tables and figures will be presented in the participant data listings. Some data may be presented only in participant data listing, some may be presented with a corresponding table or figure; these will be indicated in relevant sections below. Participants will be summarized according to treatment received.

For the purpose of all primary and secondary analyses where applicable, baseline is defined as the last measurement prior to receipt of IP.

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

13.4. Demographics and Baseline Characteristics

Demographic data, such as age, race, and ethnicity, and baseline characteristics, such as height, weight, and BMI, will be summarized using the Safety Set.

Pregnancy test results and drug screen results will be listed but not summarized.

Medical history will be listed by participant.

13.5. Efficacy Analysis

The estimand for the primary efficacy analysis is the treatment difference between SAGE-324 and placebo in mean change from baseline in clinic-based TETRAS performance subscale part 4 upper limb tremor scores at Day 29 based on the Full Analysis Set. This will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline TETRAS performance subscale part 4 upper limb tremor score, assessment timepoint, and timepoint-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline clinic visits will be included in the model. The main comparison will be between SAGE-324 and placebo at the 29-day timepoint. Model-based point estimates (ie, least squares means, 5% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-subject errors. If there is a convergence issue with the unstructured covariance model, Toeplitz compound symmetry or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not UN, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

Similar to those methods described above for the primary endpoint, an MMRM will be used for the analysis of the change from baseline in TETRAS total performance scores, Kinesia ONE accelerometer scores and TETRAS ADL scores.

Other efficacy analyses will be specified in the SAP. In general, data will be analyzed using appropriate descriptive statistics or prespecified statistical methods as applicable; participant listings will be provided for all efficacy data. Participants will be analyzed according to randomized treatment for the purpose of efficacy unless otherwise specified.

Sensitivity analyses will be described in the SAP.

13.6. Safety Analyses

Safety and tolerability of SAGE-324 will be evaluated by AEs, concomitant medication usage, [redacted] Safety data will be listed by participant and summarized by treatment group. All safety summaries will be performed on the Safety Set using treatment received.

13.6.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or higher. A treatment-emergent adverse event (TEAE) is defined as an AE with onset after the first dose of IP. The analysis of AEs will be based on the concept of TEAEs. The incidence of TEAEs will be summarized by System Organ Class (SOC) and preferred term. In addition, summaries will be provided by intensity (mild, moderate, severe) and by causality (related, not related) to IP.

Any TEAEs leading to discontinuation of treatment or withdrawal from the study and any treatment-emergent SAEs will be summarized.

All AEs and SAEs (including those with onset or worsening before the start of IP) through the end of the study will be listed.

[redacted]

13.6.3. Physical Examinations

The occurrence of a physical examination, including MSE, (yes/no) and the date performed will be listed by participant.

[redacted]

13.6.6. 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 (WHO-DD) September 2015, or later.

All medications taken within 30 days prior to informed consent through the duration of the study will be recorded. In addition, all psychotropic medications taken in the previous 30 days prior to screening will be recorded. Those medications taken prior to the initiation of the start of IP will be denoted “Prior”. Those medications taken prior to the initiation of the IP and continuing beyond the initiation of the IP or those medications started at the same time or after the initiation of the IP will be denoted “Concomitant”.

Medications will be presented according to whether they are “Prior” or “Concomitant” as defined above. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

Details of prior and concomitant medications will be listed by participant, start date, and verbatim term.

13.8. Sample Size and Power

The sample size of this study is based on the assumption of a 3 points difference in the change from baseline TETRAS performance subscale part 4 upper limb tremor score between SAGE-324 and placebo with a standard deviation of 3.5 points. Under these assumptions, a sample size of 25 evaluable participants per group would provide 85% power for detecting a placebo-adjusted treatment difference of 3 points in TETRAS performance subscale part 4 upper limb tremor score assuming a 2-sided test at an alpha level of 0.05. By including 2 treatment groups and using a 1:1 randomization, a total of 50 evaluable participants are required. Assuming a nonevaluability rate of 15%, approximately 60 participants will be randomized. Additional participants may be enrolled if the dropout rate is greater than 15%.

13.8.1. Interim and Data Monitoring Committee (DMC) Analyses

13.8.1.1. Interim Analysis

The sponsor may conduct an interim analysis. Detailed descriptions of planned data analyses will be provided in a separate interim statistical analysis plan (SAP), if applicable.

13.8.1.2. DMC Analysis

Not applicable

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of Sage Therapeutics will visit the investigational study site per Sage SOPs to:

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

During the study, a monitor from Sage Therapeutics or representative 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 case report forms, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the participant'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 participant (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Sage Therapeutics.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Sage Therapeutics and those SAEs that met criteria for reporting have been forwarded to the IRB or EC.

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

14.2. Audits and Inspections

Sage Therapeutics or authorized representatives of Sage Therapeutics, a regulatory authority, or an independent EC or an IRB may visit the site to perform an audit(s) or inspection(s), including source data verification. The purpose of a Sage Therapeutics audit or a regulatory authority 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/ICH GCP guidelines, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency or IRB/EC about an inspection.

14.3. Institutional Review Board or Ethics Committee

The principal investigator must obtain IRB (or EC) approval for the clinical study prior to enrolling a participant. Initial IRB (or EC) approval, and all materials approved by the IRB (or EC) for this study including the participant consent form and recruitment materials must be maintained by the investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practice and all applicable regulatory requirements, Sage Therapeutics may conduct a quality assurance audit(s) at the clinical site. Please see Section 14.2 for more details regarding the audit process.

The investigator must have adequate quality control practices to ensure that the study is performed in a manner consistent with the protocol, GCP/ICH GCP guidelines, and applicable regulatory requirements. The investigator is responsible for reviewing all identified protocol deviations. Significant protocol deviations should be reported to the IRB/EC per the IRB/EC's written procedures.

The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site. When the investigator retains the services of any individual or party to perform trial-related duties and functions, the investigator must ensure the individual or party is qualified to perform trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed, and any data generated.

The investigator must maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained, if necessary, to provide clarification.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF, must be given a written and dated approval or favorable opinion by an IRB or EC as appropriate. The investigator must obtain and document approval before he or she can enroll any participant into the study. The IRB or EC must supply to the sponsor a list of the IRB/EC membership and a statement to confirm that the IRB/EC is organized and operates according to GCP and applicable laws and regulations.

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

The principal investigator is also responsible for providing the IRB or EC with reports of any reportable serious adverse drug reactions from any other study conducted with the IP. Sage Therapeutics will provide this information to the principal investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or EC according to local regulations and guidelines. In addition, the principal investigator must inform the IRB/EC and sponsor of any changes significantly affecting the conduct of the trial and/or increasing the risk to participants (eg, violations to the protocol or urgent safety measures taken for participant safety).

16.2. 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 are consistent with ICH and GCP guidelines, as well as all applicable regional or national regulatory requirements.

16.3. Written Informed Consent

Prior to enrolling a trial participant, the investigator(s) will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and allowed time to consider the information provided.

When the participant decides to participate in the trial, the participant (or the participant's, parent or legally authorized representative) must provide signed and dated informed consent. The written consent must be obtained before conducting any study procedures. The investigator must document the consent process in the participant's source records. The investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant or to the participant's parent or legally authorized representative.

Throughout the trial participants should be informed of any changes made to the study and as new safety and or risk information becomes known. The provision of this information will be documented in the participant's source records, and when applicable, an updated ICF will be provided.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Sage Therapeutics or its representative(s) will be allowed to conduct site visits at the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the facility, drug storage area, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

Inspection of the study by a regulatory authority may occur at any time. The investigator must agree to the inspection of study-related records and source documents by the regulatory authority representative(s).

17.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for the period outlined in the site contract, or for a period of 2 years after the last marketing application approval, and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Sage is responsible to inform the investigator/institution as to when study documents no longer need to be retained.

18. PUBLICATION POLICY

All information concerning SAGE-324 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.

19. LIST OF REFERENCES

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324-ETD-201 Protocol Administrative Letter #1

The purpose of this letter is to notify Investigators of an upcoming protocol amendment on the management of participants experiencing adverse events of somnolence or similar events.

This letter should be submitted to the local Independent Review Board (IRB) and filed within the Investigator Site File.

The following represents the minimum action an investigator must take in response to an experience of somnolence or similar adverse events experienced by a participant. The investigator should, as always, continue to use their clinical judgement and institute drug holidays, dose reductions and IP discontinuations over and above these instructions to ensure the safety and well-being of all participants**.**

If a participant experiences moderate or severe adverse events of somnolence, drowsiness, dizziness or similar on Day 1 or at any point during the treatment period:

- The Investigator must carefully assess the participant before they leave the clinic
- The Investigator must instruct the participant prior to resuming study drug dosing via phone call or in person to ensure that:
    - The participant has a drug holiday of at least one day (they must miss at least one dose)
    - The participant's daily dose of study drug must then be reduced from 60 mg to 45 mg when study drug dosing resumes
- The Investigator must closely monitor the participant's condition via phone call or in person visit to assess the effectiveness of the drug holiday and dose reduction.

Following the first drug holiday and dose reduction, if the events persist and continue to be moderate or severe, or the participant experiences a new moderate or severe AE of somnolence, drowsiness, dizziness or similar:

- The Investigator must instruct the participant prior to resuming study drug dosing via phone call or in person to ensure that:
    - The participant has another drug holiday of at least one day (they must miss at least one dose)
    - The participant's daily dose of study drug must then be further reduced from 45 mg to 30 mg when study drug dosing resumes
- The Investigator must closely monitor the participant's condition via phone call or in person visit to assess the effectiveness of the drug holiday and dose reduction

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Following the second drug holiday and dose reduction to 30 mg, if the events persist or recur and are moderate or severe:

- The investigator must discontinue the participant from the Investigational Product (See Section 8.4.1 of Protocol: Investigational Product Discontinuation)

If at any time somnolence, drowsiness, dizziness or similar events of any severity are also associated with symptoms such as confusion or balance impairment:

- The Investigator must follow the instructions as above on drug holidays, dose reductions and IP discontinuation.

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[redacted]
Signer Name: [redacted]
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