Official Title: A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Dose-Response Study of SAGE-324 for the Treatment of Essential Tremor

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A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, DOSE-RESPONSE STUDY OF SAGE-324 FOR THE TREATMENT OF ESSENTIAL TREMOR

PROTOCOL NUMBER: 324-ETD-202

IND NUMBER: 144989

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] Email: [redacted]
Sponsor Medical Monitor	[redacted] MD [redacted] Phone/text: [redacted] E-mail: [redacted]
Date of Original Protocol	03 September 2021
Date of Amendment 1	04 March 2022
Date of Amendment 2	04 May 2022
Date of Amendment 3	07 October 2022
Date of Amendment 4	10 January 2023
Date of Amendment 5	02 November 2023

INVESTIGATOR'S AGREEMENT

I have received and read the SAGE-324 Investigator's Brochure. I have read the 324-ETD-202 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] Email: [redacted]
24-Hour Emergency Contact	[redacted] [redacted] MD, MPH	E-mail: [redacted] Phone: [redacted]
Serious Adverse Event (SAE) Reporting Contact	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
	Sage Study Physician [redacted] MD	E-mail: [redacted]
	[redacted] [redacted] MD, MPH	E-mail: [redacted]
Product Complaint Contact	Sage Therapeutics	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, Randomized, Placebo-Controlled, Dose-Response Study of SAGE-324 for the Treatment of Essential Tremor

Number of Sites and Study Location: This study will take place at approximately 60 sites worldwide

Phase of Development: 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 approximately 132 days.

Objectives and Endpoints:

Objectives	**Endpoints**
Primary	
• To evaluate the dose-response relationship of different doses of SAGE-324 on upper extremity tremor in the monotherapy cohort	• Change from baseline in The Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale Item 4 (upper limb) total score on Day 91 in the monotherapy cohort
Secondary	
• To evaluate the dose-response relationship of different doses of SAGE-324 on specified activities of daily living (ADL) in the monotherapy cohort	• Change from baseline in TETRAS ADL composite score in the monotherapy cohort
[redacted]	

[redacted]

• To assess the safety and tolerability of SAGE-324	• Incidence of treatment-emergent adverse events (TEAEs)
• To evaluate the effect of SAGE-324 on other safety parameters	• Change from baseline in vital signs, electrocardiogram (ECG), clinical laboratory parameters [redacted]

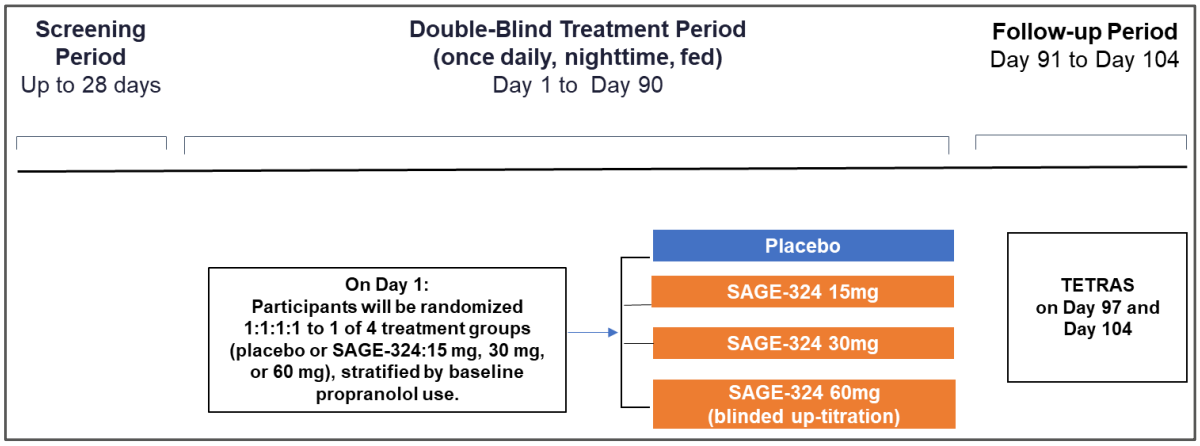
[redacted]

[redacted]

Study Description:

This is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy, safety, and tolerability of SAGE-324 in participants with ET. Participants, site staff, and sponsor personnel will be blinded to treatment allocations. The study is presented schematically in Figure 1.

Figure 1: Study Design



Abbreviation: TETRAS = The Essential Tremor Rating Assessment Scale.
Note: The Screening Period may be extended for an additional 14 days (total of 42 days) for subjects requiring additional time to taper ET medication (other than propranolol), after approval from the sponsor.

This study includes a Screening Period of up to 28 days, a 90-day double-blind Treatment Period (90 days of dosing), and a 14-day Follow-up Period. After providing informed consent, participants will undergo screening assessments to determine eligibility as outlined in Table 2.

- **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). The Screening Period may be extended for an additional 14 days (total of 42 days) for subjects requiring additional time to taper ET medication (other than propranolol), after approval from the sponsor. Following completion of screening and Day 1 eligibility assessments, participants will be randomized to 1 of 4 treatment groups (matching placebo or SAGE-324: 15 mg, 30 mg, or 60 mg, oral daily) in a 1:1:1:1 ratio, stratified by baseline propranolol use (adjunct therapy).
- **Double-Blind Treatment Period:** Starting on Day 1, after randomization, participants will receive a single dose of investigational product (IP) once daily for 90 days on an outpatient basis, to be taken before bed, with a snack if bedtime is not within 2 hours of the evening meal. Guidance on suitable snacks will be provided. During the Treatment Period, participants will return to the study center for efficacy and safety assessments as specified in Table 2. In addition, safety phone call study visits will be conducted according to Table 2, or more often as deemed appropriate by the investigator, to review the current status of the

participant. Participants will be trained on the use of software applications and devices necessary to complete questionnaires or self-rated study assessments.

Participants should gain experience with the study drug to see how it affects them before engaging in potentially hazardous activities requiring mental alertness, such as driving. If participants experience any sleepiness, dizziness, or feelings of relaxation, or have other sedative effects, they should not engage in potentially hazardous activities requiring mental alertness, such as driving, until any sleepiness/sedative effects from the study drug have dissipated. This is important because study participants may not be able to judge how these sedative effects will affect their ability to perform potentially hazardous activities requiring mental alertness, including driving.

- **Follow-Up Period:** Follow-up visits will be conducted on an outpatient basis on Days 97 and 104. Participants will continue to complete questionnaires as indicated in Table 2 and will return to the clinic approximately 6 days after the last dose of IP (ie, Day 97) for efficacy and safety monitoring. Participants will return to the study center for an End of Study (EOS) Visit approximately 13 days following the last dose of IP (ie, Day 104); the Early Termination Visit (ETV) will be conducted at the time of discontinuation if this occurs any time before Day 104.

No dose reductions of SAGE-324 will be permitted.

All participants who conclude the study will be offered the opportunity to enroll in a SAGE-324 long-term open-label study, as per the long-term open-label study's eligibility criteria.

Number of Participants (planned): Approximately 160 participants, with at least 104 (65%, 26 participants per dose group) monotherapy participants and up to 56 (35%, 14 participants per dose group) adjunct therapy participants, will be randomized to ensure at least 22 participants per arm in the monotherapy cohort will complete the study.

Eligibility Criteria:

Inclusion Criteria:

1. Participant has signed an ICF before any study-specific procedures or washout of drugs is started.
2. Participant is ambulatory and is 18 to 80 years of age, inclusive, at the time informed consent is obtained.
3. Participant is in good physical health and has no clinically significant findings (excluding ET), as determined by the investigator, on physical examination, including neurologic and mental status examinations, 12-lead ECG, or clinical laboratory tests.
4. 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).
5. 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
6. Participant has the following:
   a. Scores at least 12 in the combined TETRAS Performance Subscale Item 4 (upper limb tremor) at both Screening and predose on Day 1

b. Scores at least 6 in the total TETRAS Performance Subscale Item 4 score for the dominant upper limb (the sum of the three items for either the right or left upper limb, whichever is dominant) at both Screening and predose on Day 1.

7. Participant has a baseline TETRAS ADL Subscale score of at least 20 at Screening.
8. Participant is willing to discontinue medications taken for the treatment of ET except propranolol, 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 97. Participants in the adjunct therapy cohort must be on a stable dose of propranolol for the treatment of ET (maximum total daily propranolol dose up to 320 mg allowed) from 3 months prior to Screening through Day 97 of the study.
9. Participant is willing to limit use of alcohol to 2 units per day for males and 1 unit per day for females starting at least 1 week prior to Day 1 and through Day 97 of the study.

   A unit of alcohol is defined as: 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of distilled spirits.

   Participant will limit alcohol use to at least 2 hours before self-administration of IP in the evening.

   Participant will not use alcohol starting 24 hours prior to the scheduled in-clinic study visits until all assessments have been completed.
10. Female participant agrees to use at least one method of highly effective contraception as listed in Section 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 [FSH] >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).
11. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 13 weeks after receiving the last dose of 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.
12. Male participant is willing to abstain from sperm donation for the duration of the study and for 13 weeks after receiving the last dose of study drug.
13. Participant is willing to maintain prestudy consumption of products that contain nicotine starting at least 1 week prior to Day 1 and through Day 97 of the study.

Exclusion Criteria:

1. Participant has presence of known causes of enhanced physiological tremor.
2. Participant has had newly administered tremorgenic drugs (14 days or 5 half-lives [whichever is longer] prior to Day 1) 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. Use of Cala Trio bracelet for the treatment of ET from two weeks prior to Day 1 through Day 97 is prohibited.
5. Participant has had botulinum toxin for treatment of ET within 6 months of Screening.
6. Participant has historical or clinical evidence of tremor with functional neurological syndrome origin.

7. Participant has currently active and medically significant or uncontrolled hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, metabolic disease (hypothyroidism with stable thyroid replacement is acceptable).
8. Participant has a body weight >140 kg or a body mass index (BMI) ≥50 kg/m^2 at Screening.
9. Participant currently requires propranolol treatment for a medical condition other than ET.
10. Participant has a clinically relevant history within 3 years of Screening or ongoing oncologic disease, in the judgement of the investigator, excluding skin cancers (squamous or basal cell carcinoma) for which treatment has been completed or any carcinoma in situ.
11. Participant has history of substance abuse or dependence prior to Screening has a positive screen for drugs of abuse at Screening or predose on Day 1. Participants with nicotine use disorder that impacts their tremor are excluded.
12. Participant has a known allergy to any IP excipient.
13. Female participant has a positive pregnancy test or confirmed pregnancy or is breastfeeding.
14. Participant has had exposure to another investigational drug or device within 30 days or 5 half-lives of the investigational drug, whichever is longer, prior to the Day 1 visit.
15. [redacted]
16. Participant has donated 1 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.
17. Participant has night shift work.
18. 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.
19. Participant is unwilling or unable to comply with study procedures and required training.
20. 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 and is unwilling to refrain from taking these medications or foods for the duration of dosing. Use of mild cytochrome inhibitors and/or inducers may be permitted.
21. 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.
22. Participant plans to undergo elective surgery during participation in the study.
23. Participant is unable to complete participation in the study, eg, due to preplanned event.
24. Participant is investigative site personnel or a member of their immediate families (spouse, parent, child, or sibling whether biological or legally adopted).
25. Participant has previously participated in a SAGE-324 clinical study.

Investigational Product Therapy Dosage and Mode of Administration:

SAGE-324 will be administered orally once daily, to be taken before bed, with a snack if bedtime is not within 2 hours of the evening meal.

The 15-mg dose group will receive 15 mg of SAGE-324 from Day 1 to Day 90.

The 30-mg dose group will receive 30 mg of SAGE-324 from Day 1 to Day 90.

The 60-mg dose group will receive 15 mg of SAGE-324 from Day 1 to Day 14, then 30 mg from Day 15 to Day 28, then 45 mg from Day 29 to Day 42, and then 60 mg from Day 43 to Day 90.

Reference Therapy Dosage and Mode of Administration:

Placebo will be administered orally once daily for 90 days.

Duration of Treatment:

Each participant will receive SAGE-324 or matching placebo oral tablets for 90 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 total TETRAS Performance Subscale Item 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 planned sample size is 160 participants, randomized in a 1:1:1:1 ratio to each of the dose groups (matching placebo and SAGE-324: 15 mg, 30 mg, and 60 mg), stratified by baseline propranolol use, with at least 104 (65%, 26 participants per dose group) monotherapy participants and up to 56 (35%, 14 participants per dose group) adjunct therapy participants.

The sample size of 104 participants for the monotherapy cohort assumes a change from baseline at Day 91 in TETRAS upper limb Item 4 score for the placebo group of -1.2 points, a maximum decrease of -3.2 points from baseline for a dose response in the 15-mg to 60-mg dose groups with a standard deviation of 2.5. Under these assumptions with a few prespecified candidate dose-response models, including linear, loglinear, quadratic, exponential, logistic, Emax, sigEmax and beta, a sample size of 22 evaluable participants per group would provide 80% power for demonstrating a nonflat dose-response relationship by Multiple Comparisons and Modeling (MCP-Mod) approach,

using a 1-sided type I error rate of 0.05. Assuming a nonevaluable rate of 15% across all treatment groups, approximately 104 participants (26 per treatment group) will be randomized. Additional monotherapy participants may be enrolled if the overall nonevaluable rate is higher than 20%.

The sample size for adjunct therapy cohort is not based on statistical significance, but clinical considerations. Up to 56 adjunct therapy participants (14 per dose group) are to provide some adjunct therapy directional data on both efficacy and safety measures.

Additional participants may be randomized if the variances during the blinded interim analysis are larger than the assumptions above. However, no more than 200 participants, including adjunct therapy participants, will be randomized.

Statistical Analysis of Primary Efficacy Endpoint

The estimand for the primary and secondary efficacy endpoint is defined as follows:

1. There are 4 treatment groups for the monotherapy participants to be evaluated: SAGE-324 (15 mg, 30 mg, 60 mg) and placebo.
2. The target population consists of the monotherapy participants ages 18 to 80 years and have a diagnosis of ET with combined total upper limb TETRAS Performance Subscale Item 4 of at least 12 with the dominant upper limb score of at least 6 and baseline TETRAS ADL score of at least 20.
3. The outcome for the primary efficacy endpoint is the change from baseline in TETRAS Performance Subscale Item 4 score on Day 91.
4. The population-level summary measure is the dose-response of different doses of SAGE-324 and placebo for the monotherapy cohort.
5. The treatment/hypothetical policy strategy will be adopted for the primary and secondary endpoint. For data collected after the intercurrent events, such as rescue medication, the treatment policy strategy will be used. For data not available after the intercurrent events, like premature discontinuation of study treatment, the hypothetical policy strategy will be adopted. This means that the dose-responses of different dose groups will be analyzed using all observed on-study data, regardless of the occurrence of the intercurrent event, including use of additional medication, premature discontinuation of treatment for any reason, or other protocol violations.

This will first be analyzed using a mixed-effects model for repeated measures (MMRM); the model will include treatment, baseline TETRAS Performance Subscale Item 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. An unstructured covariance structure will be used to model the within-participant errors. If there is a convergence issue with the unstructured covariance model, Toeplitz 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.

After the MMRM analysis by PROC MIXED, the estimated mean and covariance matrix will be passed to the MCP-Mod analysis to test the dose-response relationship. In the analysis, multiple dose-response candidate models will be prespecified. The actual dose-response relationship will be assessed using the estimated means and covariance matrix from MMRM analysis. A critical value will be determined from the joint multivariate normal distribution of the contrast test statistics at the overall one-sided alpha level of 0.05. If the test statistic exceeds this critical value, a nonflat dose-response relationship will be demonstrated.

Secondary efficacy endpoints will be analyzed similarly to the primary endpoint.

Safety Analysis

Safety and tolerability of study drug will be evaluated in each stratum (monotherapy cohort and adjunct therapy cohort) and overall using incidence of TEAEs/serious adverse events [redacted] and changes from baseline in vital signs, clinical laboratory evaluations, 12-lead ECG [redacted]. [redacted] Safety data will also be listed by participant using the Safety Set.

[redacted]

Interim Analysis

A blinded interim look at the primary and secondary endpoint data may be conducted to evaluate the sample size assumptions.

Table 2: Schedule of Assessments

Assessment	Screening	Treatment Period													Follow-up Period	
Study Day	**-28 to -1**	**1**	**3 (±1)**	**8 (±1)**	**15 (±1)**	**19 (±1)**	**29 (±1)**	**33 (±1)**	**43 (±1)**	**47 (±1)**	**57 (±3)**	**71 (±3)**	**80 (±3)**	**91 (+1) EOT**	**97 (±3)**	**104 (±3) EOS/ETV**
Clinic Visit (CV)/Phone Call (PC)	**CV**	**CV**	**PC**	**CV**	**CV**	**PC**	**CV**	**PC**	**CV**	**PC**	**CV**	**CV**	**PC**	**CV**	**CV**	**CV**
Informed consent	X															
Inclusion/Exclusion	X	X														
Demographics	X															
Medical history	X	X														
Pregnancy test	X (serum; all women)	X (urine; WOCBP only)			X (urine; WOCBP only)	/			X (urine; WOCBP only)					X (urine; WOCBP only)		X (urine; WOCBP only)
FSH (postmenopausal women only)	X															
Randomization [a]		X														
Drug screen	X	X														
Complete physical examination, including neurological examination including MSE [b]	X													X		X
Body height	X															
Body weight	X	X														X
Vital signs [c]	X	X		X	X		X		X		X	X		X	X	X
12-Lead ECG [d]	X	X					X							X		X
Chemistry/hematology/ coagulation/urinalysis[e]	X	X		X	X		X		X		X	X		X		X

Assessment	Screening	Treatment Period													Follow-up Period	
Study Day	**-28 to -1**	**1**	**3 (±1)**	**8 (±1)**	**15 (±1)**	**19 (±1)**	**29 (±1)**	**33 (±1)**	**43 (±1)**	**47 (±1)**	**57 (±3)**	**71 (±3)**	**80 (±3)**	**91 (+1) EOT**	**97 (±3)**	**104 (±3) EOS/ETV**
[redacted]																
TETRAS [g h]	X	X		X	X		X		X		X	X		X	X	
[redacted]																

Assessment	Screening	Treatment Period													Follow-up Period	
Study Day	**-28 to -1**	**1**	**3 (±1)**	**8 (±1)**	**15 (±1)**	**19 (±1)**	**29 (±1)**	**33 (±1)**	**43 (±1)**	**47 (±1)**	**57 (±3)**	**71 (±3)**	**80 (±3)**	**91 (+1) EOT**	**97 (±3)**	**104 (±3) EOS/ETV**
Participant training[i]	X	X														
Dispense IP		X			X		X		X		X	X				
IP administration[j]		Administered once daily before bed on Day 1 through Day 90														
AEs/SAEs, including COVID-19 assessments[k]	X															
Prior medication and history[l]	X															
Concomitant medication, diet, alcohol, and nicotine products		X														

Abbreviations: AE = adverse event; [redacted] COVID-19 = coronavirus disease 2019; [redacted] ECG = electrocardiogram EOS = end of study; EOT = end of treatment; [redacted] ET = essential tremor; ETV = early termination visit; FSH = follicle stimulating hormone; ICF = informed consent form; 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: The suggested order of assessments during clinic visits is vital signs, TETRAS, ECG, blood sample collection for [redacted] clinical laboratory assessments, and questionnaires.

Note: If necessary, screening assessments may be split between 2 visits in order to allow enough time for washout or down-titration and washout of prior ET therapy except propranolol during the Screening Period.

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

[b] Complete physical examinations and a comprehensive neurological examination, including MSEs, should be performed at Screening and EOT and as clinically necessary (see Section 12.1.3). Targeted physical and neurological examinations should be performed at other times as indicated by AEs.

[c] 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 on Day 1.

[d] ECGs will be collected and read centrally. All ECGs must be performed after the participant has been in a supine position for at least 5 minutes.

[e] Chemistry, hematology, coagulation, and urinalysis to be collected at all timepoints except Day 97. Note: Myoglobin (urinalysis) and serum creatine kinase (biochemistry) will be collected at Screening. In addition, myoglobin (urinalysis) and serum creatine kinase (biochemistry) may be collected at any additional timepoints at the discretion of the investigator (including Day 97). A serum sample for blood alcohol level will be collected at all timepoints (including Day 97). HbA1c will be collected at Screening and EOS/ETV Visit only.

[redacted]

[g] A videographer will record TETRAS administration at Screening.
[h] Washout of prestudy ET drug(s) except propranolol after the ICF was signed (Section 9.2.2.1) must be completed prior to Screening TETRAS assessment.
[i] Participants will be trained by study personnel on the use of software applications, IP diary, and devices necessary for the conduct of the study.
[j] Will be administered once daily, to be taken before bed, with a snack if bedtime is not within 2 hours of the evening meal. The 60-mg dose group will receive 15 mg SAGE-324 from Day 1 to Day 14, then 30 mg from Day 15 to Day 28, then 45 mg from Day 29 to Day 42, and then 60 mg from Day 43 to Day 90.
[k] 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.
[l] Including 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.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 3: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	adverse event
ADL	activities of daily living
AR(1)	Autoregressive (1)
BMI	body mass index
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
COVID-19	coronavirus disease 2019
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End of Study
EOT	End of Treatment
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ET	essential tremor
ETV	Early Termination Visit
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
$GABA_A$	γ-aminobutyric acid-gated chloride channel
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference for Harmonisation
ID	identification
IEC	Independent Ethic Committee
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology

Abbreviation	Definition
MCP-Mod	Multiple Comparisons and Modeling
MMRM	mixed-effects model for repeated measures
MR	magnetic resonance
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
QTcF	QT corrected according to Fridericia's formula
SAP	statistical analysis plan
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
UP	Unanticipated Problem
USM	Urgent Safety Measure
[redacted]	[redacted]
WOCBP	woman of childbearing potential

5. INTRODUCTION

SAGE-324 is a positive allosteric modulator of A-type γ-aminobutyric acid-gated chloride channel ($GABA_A$) receptors, the major class of inhibitory neurotransmitter receptors in the brain. SAGE-324 is planned to be evaluated for multiple indications affected by activity at the $GABA_A$ receptor, including essential tremor (ET).

Clinical studies of SAGE-324 in healthy adults and in adults with ET, in addition to preclinical studies of SAGE-324, are detailed in the SAGE-324 investigator's brochure as well as a detailed description of the chemistry, pharmacology, efficacy, and safety of SAGE-324.

ET is a common, permanently debilitating, neurologically determined movement disorder characterized by involuntary rhythmic oscillation of a body part due to intermittent muscle contractions. This shaking typically occurs during voluntary movement (ie, 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 United States and worldwide, 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 terms 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.

Current first-line therapies, propranolol and primidone, are the most commonly used medications for the treatment of ET. These therapies reduce tremor by >50% in 40% of people (Koller 1994), while up to 30% of patients do not respond to first-line therapy or experience intolerable adverse effects (Koller 1989). The only Food and Drug Administration (FDA)-approved pharmacological treatment for ET is propranolol, a β-adrenergic receptor antagonist. Because of its non-selective mechanism of action, not all individuals with ET are able to take propranolol due to contraindications such as asthma, heart failure, and diabetes (propranolol Prescribing Information). In addition, propranolol is not always well tolerated, mainly due to fatigue and similar adverse reactions, as well as rare serious adverse reactions (Olanow 2008, Wyeth 2010). Secondary pharmacologic approaches to the treatment of ET have included off-label use of anticonvulsants with limited GABA activity (eg, topiramate, gabapentin) and the use of alcohol (Rajput 2014). Notably, tolerability is a key limiting factor of propranolol, primidone, and similar therapies utilized by ET patients.

Five clinical pharmacology studies (324-CLP-101, 324-CLP-102, 324-CLP-104, 324-CLP-105, and 324-CLP-106) and 1 efficacy study (324-ETD-201) are complete. The results of these clinical studies suggest that SAGE-324 may safely ameliorate symptoms in patients suffering from ET.

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. Hence, 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 15, 30, and 60 mg doses of SAGE-324 on outcome measures specific to ET [redacted].

5.1. Dose Justification

Sage has completed 2 studies of SAGE-324 in participants with ET with promising results: a Phase 1 open-label, single, ascending-dose study (324-CLP-101) and a Phase 2 double-blind study (324-ETD-201) of once daily 60 mg of SAGE-324 or placebo for 28 days.

One dose (60 mg), the highest dose from the 324-CLP-101 study, was evaluated in Study 324-ETD-201 to maximize the chance of seeing a pharmacodynamic effect. Study 324-ETD-201 met its prespecified primary endpoint while somnolence was the most common adverse event (AE) reported.

The present study (324-ETD-202) is a 90-day, placebo-controlled, dose-ranging study of 15, 30, and 60 mg of SAGE-324 in participants with moderate to severe ET. Given the safety and efficacy profile of SAGE-324 to date, the widest possible exposure range of doses over a 90-day period will be administered in order to determine the optimal balance of efficacy and tolerability over a wide range of doses.

In order to mitigate the AE of somnolence that was observed in Study 324-ETD-201, nighttime dosing will be employed for all 3 doses as well as an up-titration to the 60 mg dose (Section 7.3). Up-titration is a standard practice that is designed to allow participants to accommodate to the AE as plasma concentrations rise more slowly than they would if the target dose was administered from the start.

5.2. Benefit/Risk Assessment

Potential benefits and risks anticipated in this study are based on available data from 5 completed clinical pharmacology studies (324-CLP-101, 324-CLP-102, 324-CLP-104, 324-CLP-105, and 324-CLP-106) and 1 completed efficacy study (324-ETD-201), as well as toxicology studies of SAGE-324. Available nonclinical and clinical data are summarized in the SAGE-324 investigator's brochure.

Based on the mechanism of action of SAGE-324 and the results of completed nonclinical and clinical studies of SAGE-324, participants receiving SAGE-324 may have tremor reduction and improved quality of life. There is also currently no evidence of any interaction(s) (drug-drug or other, including propranolol) except for those outlined in the inclusion/exclusion criteria.

In a Phase 2, randomized, double-blind, placebo-controlled study (324-ETD-201), a statistically significant treatment difference for SAGE-324 versus placebo was observed for the primary efficacy endpoint (-1.07; 95% confidence interval: -2.14 to 0.00; $p = 0.0491$), and clinically meaningful effects were reported by participants. In addition, the sensitivity analyses showed consistency of the primary endpoint results, and subgroup analyses demonstrated a treatment difference for SAGE-324 versus placebo for most subgroups. Also, a statistically significant

reduction from baseline in The Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale item 4 upper limb tremor score at Day 29 was observed in a population with baseline upper limb tremor score of ≥12 ($p = 0.0066$). Overall, the primary endpoint analyses have demonstrated potentially positive and therapeutic effects of SAGE-324 in participants suffering from ET.

In clinical experience to date, treatment-emergent adverse events (TEAEs) of somnolence, feeling of relaxation, and dizziness have been most frequently reported. Most of the somnolence, dizziness, and feeling of relaxation events were mild or moderate. Severe serious adverse events (SAEs) of mental status changes were considered related to investigational product (IP) by the investigators. Some of reported events required dose reduction or study discontinuation but all events resolved without sequalae or requiring treatment. Participants in the current study will be dosed at nighttime and a blinded up-titration to the highest dose (60 mg) will be employed to mitigate the most commonly reported AE of somnolence in previous studies. Study participants will be closely monitored during scheduled visits, via phone calls in between clinic visits, or more frequently for AE monitoring as appropriate.

Given the outcome of the Phase 2 study and the unmet need in the treatment of ET, further investigation of SAGE-324 in patients with ET is justified based on a favorable benefit-risk profile.

6. STUDY OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary	
• To evaluate the dose-response relationship of different doses of SAGE-324 on upper extremity tremor in the monotherapy cohort	• Change from baseline in The Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale Item 4 (upper limb) total score on Day 91 in the monotherapy cohort
Secondary	
• To evaluate the dose-response relationship of different doses of SAGE-324 on specified activities of daily living (ADL) in the monotherapy cohort	• Change from baseline in TETRAS ADL composite score in the monotherapy cohort
[redacted]	

Objectives	**Endpoints**
• To assess the safety and tolerability of SAGE-324	• Incidence of treatment-emergent adverse events (TEAEs)
• To evaluate the effect of SAGE-324 on other safety parameters	• Change from baseline in vital signs, electrocardiogram (ECG), clinical laboratory parameters [redacted]

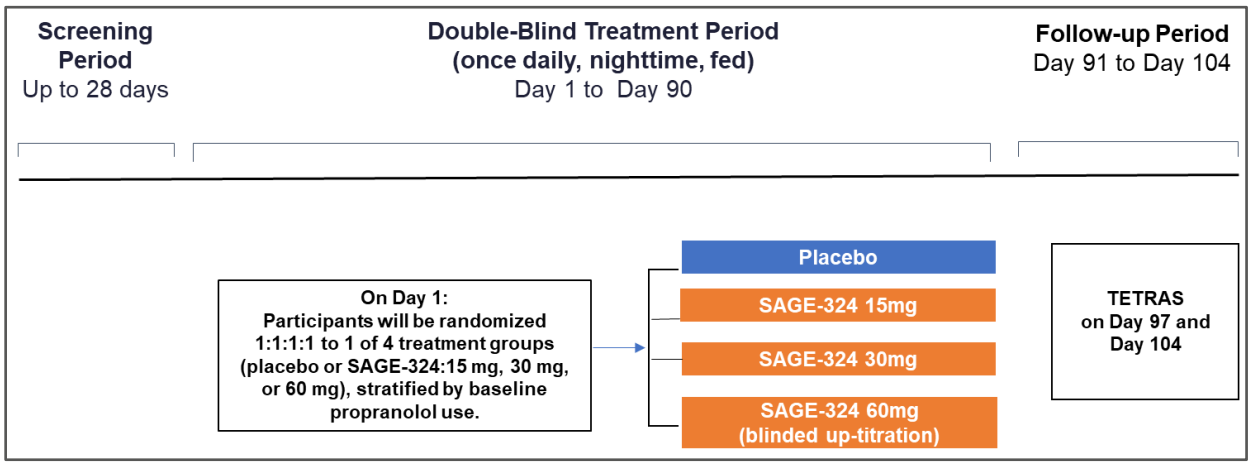
[redacted]

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This study is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy, safety, and tolerability of SAGE-324 in participants with ET. Participants, site staff, and sponsor personnel will be blinded to treatment allocations. The study is schematically presented in Figure 2.

Figure 2: Study Design



Abbreviation: R = TETRAS = The Essential Tremor Rating Assessment Scale
Note: The Screening Period may be extended for an additional 14 days (total of 42 days) for subjects requiring additional time to taper ET medication (other than propranolol), after approval from the sponsor.

This study includes a Screening Period of up to 28 days, a 90-day double-blind Treatment Period (90 days of dosing), and a 14-day Follow-up Period. After providing informed consent, participants will undergo screening assessments to determine eligibility as outlined in Table 2.

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). The Screening Period may be extended for an additional 14 days (total of 42 days) for subjects requiring additional time to taper ET medication (other than propranolol), after approval from the sponsor. Following completion of screening and Day 1 eligibility assessments, participants will be randomized to 1 of 4 treatment groups (placebo or SAGE-324: 15 mg, 30 mg, or 60 mg, oral daily) in a 1:1:1:1 ratio, stratified by baseline propranolol use (adjunct therapy).

Double-Blind Treatment Period: Starting on Day 1, after randomization, participants will receive a single dose of IP once daily for 90 days on an outpatient basis, to be taken before bed, with a snack if bedtime is not within 2 hours of the evening meal. Guidance on suitable snacks will be provided. During the Treatment Period, participants will return to the study center for efficacy and safety assessments as specified in Table 2. In addition, safety phone call study visits will be conducted according to Table 2, or more often as deemed appropriate by the investigator, to review the current status of the participant. Participants will be trained on the use of software applications and devices necessary to complete questionnaires or self-rated study assessments.

Participants should gain experience with the study drug to see how it affects them before engaging in potentially hazardous activities requiring mental alertness, such as driving. If participants experience any sleepiness, dizziness, or feelings of relaxation, or have other sedative effects, they should not engage in potentially hazardous activities requiring mental alertness, such as driving, until any sleepiness/sedative effects from the study drug have dissipated. This is important because study participants may not be able to judge how these sedative effects will affect their ability to perform potentially hazardous activities requiring mental alertness, including driving.

Follow-up Period: Follow-up visits will be conducted on an outpatient basis on Days 97 and 104. Participants will continue to complete questionnaires as indicated in Table 2 and will return to the clinic approximately 6 days after the last dose of IP (ie, Day 97) for efficacy and safety monitoring. Participants will return to the study center for an End of Study (EOS) visit approximately 13 days following the last dose of IP (ie, Day 104); the EOS visit will be conducted at the time of discontinuation if this occurs any time before Day 104.

No dose reductions of SAGE-324 will be permitted.

All participants who conclude the study will be offered the opportunity to enroll to a SAGE-324 long-term open-label study, as per the long-term open-label study's eligibility criteria.

7.2. Number of Participants

Approximately 160 participants, with at least 104 (65%, 26 participants per dose group) monotherapy participants and up to 56 (35%, 14 participants per dose group) adjunct therapy participants, will be randomized to ensure at least 22 participants per arm in the monotherapy cohort will complete the study.

7.3. Treatment Assignment

This is a randomized, double-blind, placebo-controlled study. Participants will be randomized in a 1:1:1:1 ratio to treatment groups (15 mg, 30 mg, 60 mg SAGE-324, or placebo), stratified by baseline propranolol use.

SAGE-324 or matching placebo will be administered orally once daily, to be taken before bed, with a snack if bedtime is not within 2 hours of the evening meal.

The placebo dose group will receive matching placebo from Day 1 to Day 90.

The 15-mg SAGE-324 dose group will receive 15 mg of SAGE-324 from Day 1 to Day 90.

The 30-mg SAGE-324 dose group will receive 30 mg of SAGE-324 from Day 1 to Day 90.

The 60-mg SAGE-324 dose group will receive 15 mg of SAGE-324 from Day 1 to Day 14, then 30 mg from Day 15 to Day 28, then 45 mg from Day 29 to Day 42, and then 60 mg from Day 43 to Day 90.

7.4. Dose Adjustment Criteria

Dose adjustments are not allowed in this study.

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/SAEs 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC), where required, and initiate withdrawal procedures for participating participants.

7.6. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study. A participant is considered to have completed the study if he/she has completed all phases of the study including the Day 104 visit.

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 informed consent form (ICF) before any study-specific procedures or washout of drugs is started.
2. Participant is ambulatory and is 18 to 80 years of age, inclusive, at the time informed consent is obtained.
3. Participant is in good physical health and has no clinically significant findings (excluding ET), as determined by the investigator, on physical examination, including neurologic and mental status examinations, 12-lead ECG, or clinical laboratory tests.
4. 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).
5. 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.
6. Participant has the following:
    a. Scores at least 12 in the combined TETRAS Performance Subscale Item 4 (upper limb tremor) at both Screening and predose on Day 1
    b. Scores at least 6 in the total TETRAS Performance Subscale Item 4 score for the dominant upper limb (the sum of the three items for either the right or left upper limb, whichever is dominant) at both Screening and predose on Day 1.
7. Participant has a baseline TETRAS ADL Subscale score of at least 20 at Screening.
8. Participant is willing to discontinue medications taken for the treatment of ET except propranolol 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 97. Participants in the adjunct therapy cohort must be on a stable dose of propranolol (maximum total daily propranolol dose up to 320 mg allowed) for the treatment of ET from 3 months prior to Screening through Day 97 of the study.
9. Participant is willing to limit use of alcohol to 2 units per day for males and 1 unit per day for females starting at least 1 week prior to Day 1 and through Day 97 of the study.

    A unit of alcohol is defined as: 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of distilled spirits.

    Participant will limit alcohol use to at least 2 hours before self-administration of IP in the evening.

Participant will not use alcohol starting 24 hours prior to the scheduled in-clinic study visits until all assessments have been completed.

10. 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 [FSH] >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).
11. Male participant agrees to use an acceptable method of effective contraception for the duration of the study and for 13 weeks after receiving the last dose of 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.
12. Male participant is willing to abstain from sperm donation for the duration of the study and for 13 weeks after receiving the last dose of study drug.
13. Participant is willing to maintain prestudy consumption of products that contain nicotine starting at least 1 week prior to Day 1 and through Day 97 of the study.

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 newly administered tremorgenic drugs (14 days or 5 half-lives [whichever is longer] prior to Day 1) 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. Use of Cala Trio bracelet for the treatment of ET from two weeks prior to Day 1 through Day 97 is prohibited.
5. Participant has had botulinum toxin for treatment of ET within 6 months of Screening.
6. Participant has historical or clinical evidence of tremor with functional neurological syndrome origin.
7. Participant has currently active and medically significant or uncontrolled hepatic, renal, cardiovascular, pulmonary, gastrointestinal, hematological, immunologic, metabolic disease (hypothyroidism with stable thyroid replacement is acceptable).
8. Participant has a body weight >140 kg or a body mass index (BMI) ≥50 kg/m^2 at Screening.
9. Participant currently requires propranolol treatment for a medical condition other than ET.

10. Participant has a clinically relevant history within 3 years of Screening or ongoing oncologic disease, in the judgement of the investigator, excluding skin cancers (squamous or basal cell carcinoma) for which treatment has been completed or any carcinoma in situ.
11. Participant has history of substance abuse or dependence prior to Screening has a positive screen for drugs of abuse at Screening or predose on Day 1. Participants with nicotine use disorder that impacts their tremor are excluded.
12. Participant has a known allergy to any IP excipient.
13. Female participant has a positive pregnancy test or confirmed pregnancy or is breastfeeding.
14. Participant has had exposure to another investigational drug or device within 30 days or 5 half-lives of the investigational drug, whichever is longer, prior to the Day 1 visit.

[redacted]

16. Participant has donated 1 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.
17. Participant has night shift work.
18. 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.
19. Participant is unwilling or unable to comply with study procedures and required training.
20. 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 and is unwilling to refrain from taking these medications or foods for the duration of dosing. Use of mild cytochrome inhibitors and/or inducers may be permitted.
21. 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.
22. Participant plans to undergo elective surgery during participation in the study.
23. Participant is unable to complete participation in the study, eg, due to preplanned event.
24. Participant is investigative site personnel or a member of their immediate families (spouse, parent, child, or sibling whether biological or legally adopted).
25. Participant has previously participated in a SAGE-324 clinical study.

8.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. 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 if reason for screen failure was not due to ineligible TETRAS score.

8.4. Investigational Product Discontinuation and 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 and/or from IP for safety, behavioral, compliance, or administrative reasons.

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.

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 End of Treatment (EOT) Visit, the Follow-up Visit 7 days later, and then, after a further 7 days, the EOS/Early Termination Visit (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 source documentation and recorded in the participant's 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

At the time of study withdrawal, if possible, an ETV should be conducted. Regardless of period, 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.

Reasons for study discontinuation include, but are not limited to, the following:

- Adverse event
- Pregnancy
- Protocol deviation
- Lost to follow-up
- Withdrawal by participant
- Screen failure
- Study terminated by sponsor

8.4.3. Loss to Follow-up

A participant will be deemed lost to follow-up after unsuccessful documented attempts to contact the participant

8.4.4. Replacement of Participants

Participants will not be replaced.

Additional monotherapy participants may be enrolled at the discretion of the sponsor to achieve at least 22 evaluable participants per dose group.

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 (15 mg, 30 mg, or 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 will be recorded. In addition, all psychotropic medications taken in the previous 30 days prior to Screening will be recorded. The start and end dates, route, dose/units, and frequency for all medications for ET taken at any time prior to signing the informed consent are also recorded.

All medications and/or supplements taken from the dosing of IP on Day 1 through the end of the study (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:

- Any estrogen-containing products that are widely absorbed into the systemic circulation (eg, oral, transdermal, transvaginal, etc.), used for any indication, are prohibited from Day -14 and during the study.
- 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.
- New treatment with tremorgenic drugs within 14 days or 5 half-lives (whichever is longer) of Day 1 or during the study. Continued use of established treatment with tremorgenic drugs is permitted if there is no evidence of previous or current concerns for these medications to cause or exacerbate tremor as determined by investigator.
- Use of agents known to affect SAGE-324 drug metabolism (any known moderate or severe cytochrome P450 3A4 inhibitors and/or inducers) within 14 days or 5 half-lives (whichever is longer) of Day 1 and through Day 90 of the study period. Use of mild cytochrome 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 90-day dosing period.
- As needed [PRN] propranolol use during the study.

9.2.2.1. Prestudy Essential Tremor Medications Washout

- Any prior ET medications other than propranolol must be discontinued prior to the Screening TETRAS:
  - There must be at least 14 days or 5 half-lives (whichever is longer) washout period prior to the Day 1 (baseline) visit.
  - For drugs requiring down-titration, there must be the required number of days for down-titration plus 14 days or 5 half-lives (whichever is longer) prior to the Day 1 (baseline) visit.
  - If necessary, screening assessments may be split between 2 visits in order to allow enough time for washout or down-titration and washout of prior ET therapy during the screening period.
- Prior ET medications may be restarted following Day 97 of the study.
- Participants in the adjunct therapy cohort must be on a stable dose of propranolol (maximum total daily propranolol dose up to 320 mg allowed) from 3 months prior to Screening through Day 97 of the study (no additional propranolol as needed [PRN] is allowed).

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 is limited to 2 units per day for males and 1 unit per day for females starting at least 1 week prior to Day 1 and through Day 97 of the study.

  A unit of alcohol is defined as: 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of distilled spirits.

  Participant will limit alcohol use to at least 2 hours before self-administration of IP in the evening.

  Participant will not use alcohol starting 24 hours prior to the scheduled in-clinic study visits until all assessments have been completed.
- Participants should gain experience with the study drug to see how it affects them before engaging in potentially hazardous activities requiring mental alertness, such as driving. If participants experience any sleepiness, dizziness, or feelings of relaxation, or have other sedative effects, they should not engage in potentially hazardous activities requiring mental alertness, such as driving, until any sleepiness/sedative effects from the study drug have dissipated. This is important because study participants may not be able to judge how these sedative effects will affect their ability to perform potentially hazardous activities requiring mental alertness, including driving.
- Use of products that contain nicotine is maintained at prestudy levels starting at least 1 week prior to Day 1 and through Day 97 of the study period. Participants with nicotine use disorder that impacts their tremor are excluded.

- 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 90 of the study period is prohibited.
- Use of stimulants, highly caffeinated beverages, or dietary supplements containing high doses of caffeine within 14 days or five half-lives, whichever is longer, prior to the Day 1 visit and through Day 90 of the study period is prohibited. Note: participants should not increase their regular daily consumption of caffeine during the study period.
- The use of medications other than fexofenadine for chronic allergies is recommended during participation in the study.
- Use of Cala Trio bracelet for the treatment of ET from two weeks prior to Day 1 through Day 97 is prohibited.

9.2.4. Acceptable Forms of Contraception

As per the Clinical Trials Facilitation and Coordination Group (CTFG), a woman is considered of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in females not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A male is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Acceptable forms of highly effective contraception (ie, can achieve a failure rate of <1% per year when used consistently and correctly) for participants of childbearing potential or for partners of male participants who are of childbearing potential include the following list.

- Progestogen-only oral, injectable, intravaginal, implantable, or transdermal hormonal contraception associated with inhibition of ovulation. The use of estrogen-containing contraceptives that are widely absorbed into the systemic circulation are prohibited.
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion or bilateral tubal ligation (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)

Acceptable forms of contraception which may not be considered as highly effective include:

- Oral progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable

9.3. Intervention after the End of the Study

All participants who conclude the study will be offered the opportunity to enroll in a SAGE-324 long-term open--label study, as per the long-term open-label study's eligibility criteria.

9.4. Treatment Adherence

Participants will be dispensed IP starting on Day 1 and at each clinic visit for use at home prior to the next clinic visit with instructions specifying that IP is to be administer before bed, with a snack if bedtime is not within 2 hours of the evening meal. 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.

Patients will be asked to record the dates and times of their IP dose administrations at home in a diary. They will also record the number of tablets taken and if it was taken with food.

9.5. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled study. Participants will be randomized in a 1:1:1:1 ratio to treatment groups (15 mg, 30 mg, 60 mg SAGE-324, or placebo) stratified by baseline propranolol use (adjunct therapy). Participants, site staff, and the sponsor will be blinded to treatment allocation (see study schematic in Figure 2).

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 the sponsor prior to unblinding the IP administered to a participant. Requests from the investigator about the treatment administered to study participants should be discussed with the medical monitor. If the unblinding occurs without the sponsor's knowledge, the investigator must notify the sponsor 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 study personnel are unblinded, pertinent information (including the reason for unblinding) must be documented in the participant's source documentation and in the IRT. At the time of withdrawal from the study/stopping participation, if possible, an EOT and/or ETV should be conducted.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

Table 4: 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 SAGE-324, 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

Oral SAGE324 and placebo tablets will be packaged in blinded, high-density polyethylene containers. The containers used for SAGE-324 and placebo will be identical in appearance. The package labeling conforms to FDA and Good Manufacturing Practice 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. 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, compounding (if applicable), 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 at home as specified in the Schedule of Assessments (Table 2). All participants will take 4 tablets per day in a mix of active and placebo tablets to achieve a dose of 15 mg (1 SAGE-324 tablet and 3 placebo tablets per dose), 30 mg (2 SAGE-324 tablets and 2 placebo tablets per dose), or 60 mg (4 SAGE-324 tablets). IP will be orally administered once daily before bed, with a snack if bedtime is not within 2 hours of the evening meal.

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.

Site staff will access the interactive response technology (IRT) at the Screening Visit to obtain a participant identification (ID) number for each participant that 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 IP ID number for the IP to be dispensed to that participant. The IP ID number and the number of tablets dispensed must be recorded.

At subsequent IP-dispensing visits, the investigator or designee will access the IRT, providing the same participant ID number assigned at Screening, to obtain the IP ID number for the IP to be dispensed at that visit. The IP ID number, the number of tablets dispensed, and the number of tablets returned by the participant at each 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 will be returned to Sage Therapeutics for destruction or destroyed locally per the site's procedures; disposition of IP will be documented.

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 [redacted]

11.1. Efficacy Assessments

11.1.1. The Essential Tremor Rating Assessment Scale

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

The TETRAS ADL Subscale and the TETRAS Performance Subscale will both be assessed at each clinic visit as specified in the Schedule of Assessments under TETRAS (Table 2).

The Performance Subscale assesses overall rating of tremor in the voice, limbs, head, face, trunk, while performing prespecified 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 Item 4 upper limb tremor of the Performance Subscale, all 3 maneuvers in the upper limb assessments (subscale items 4a, 4b, and 4c) will be completed for both arms, first for the right arm and then for the left. Item 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.

The ADL Subscale assesses how ET affects typical ADL (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 ADL composite endpoint comprises Items 1 to 11 of the ADL Subscale and Item 6 of the Performance Subscale.

Responses of 0 and 1 in TETRAS ADL Subscale item 1 to 11 and performance Subscale 6 will be collapsed and analyzed as a single response of 0 = normal/slightly abnormal such that the scale becomes:

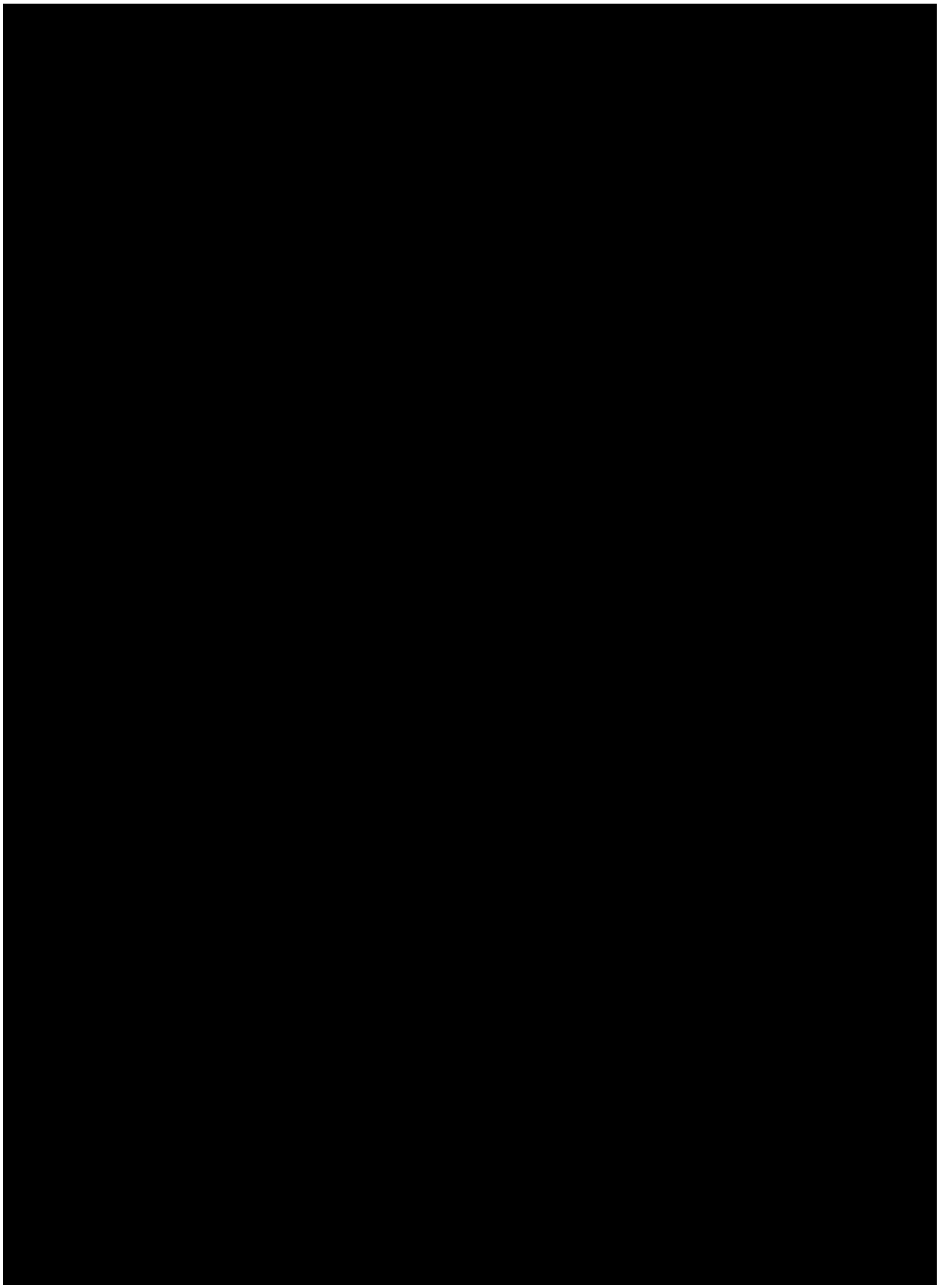
0 = Normal/slightly abnormal
1 = Mildly abnormal
2 = Moderately abnormal
3 = Severely abnormal

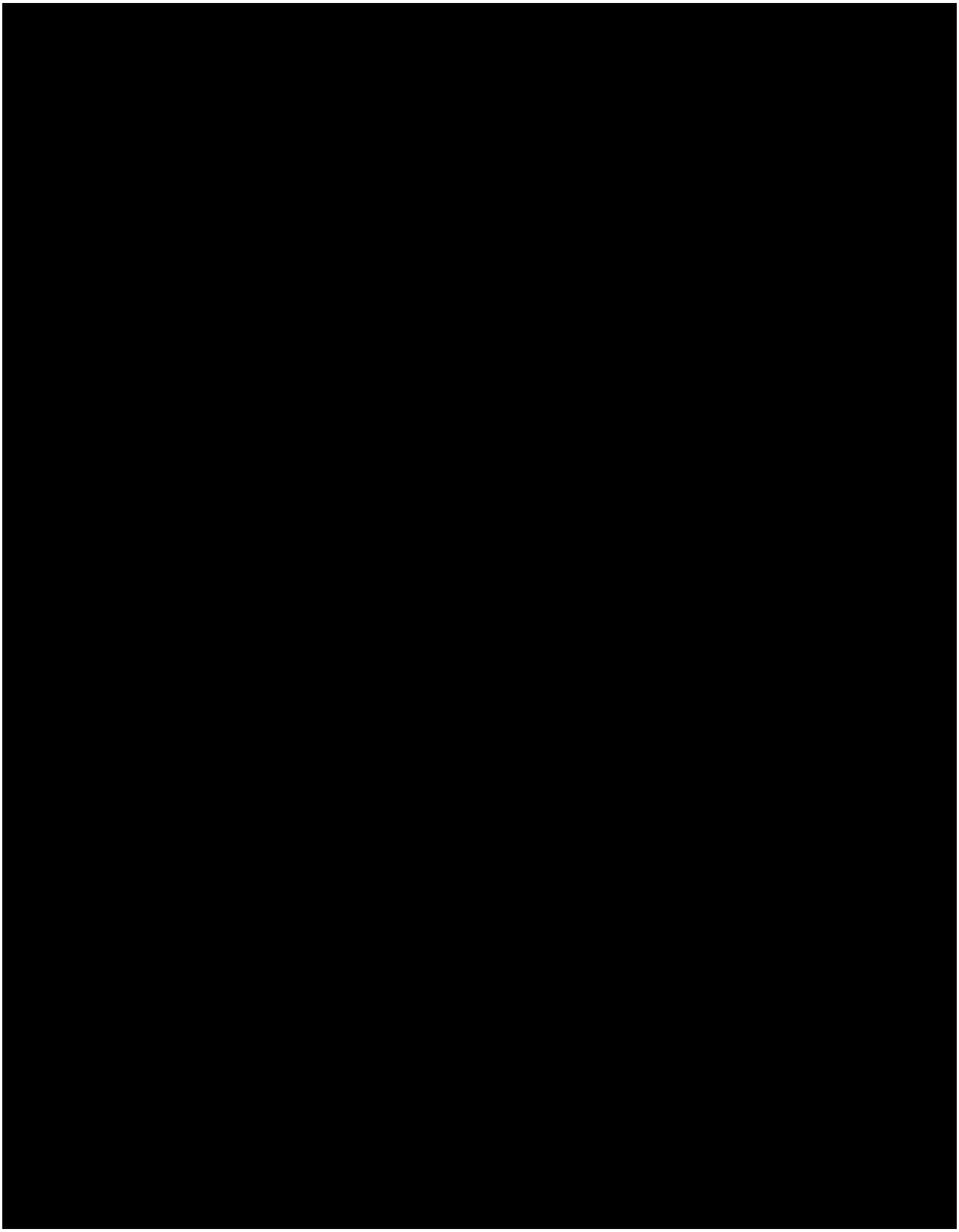
In this study, a videographer will videotape TETRAS administration at Screening.

Every effort should be made for the same rater to perform all TETRAS assessments for an individual participant and where possible, other assessments conducted by a separate site personnel.

Prior medications for ET must be discontinued prior to Screening TETRAS ratings (see Section 9.2.2.1 for washout periods).

[redacted]





[redacted]

11.2.2. Pharmacodynamic Assessments

Not applicable.

[redacted]

12. SAFETY ASSESSMENTS

12.1. Safety Parameters

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

Any abnormality in physical examinations, vital signs, ECGs, or clinical laboratory test results outside of the normal range will be interpreted by an investigator as clinically significant or not clinically significant in source documents.

12.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, ethnicity) and a full medical history, including concomitant medications and supplements, products that contain nicotine, and alcohol use, will be documented.

12.1.2. Weight and Height

Height and weight will be measured and documented. BMI will be calculated and documented.

12.1.3. Physical Examination

Complete physical examinations and a comprehensive neurological examination, including mental state examinations, should be performed at Screening and EOT and as clinically necessary. Whenever possible, the same individual should perform all physical examinations. Complete physical examinations will include assessment of body systems (eg, head, eyes, ears, nose, and throat; heart; lungs; abdomen; and extremities) as well as cognitive and neurological examination and mental status examination. Targeted physical and neurological examinations should be performed at other times as indicated by AEs, per the investigator's discretion.

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. 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. On Day 1, supine and standing blood pressure and heart rate will be collected in triplicate at least 15 minutes apart.

12.1.5. Electrocardiogram

A 12-lead ECG will be performed. The standard intervals (heart rate, PR, QRS, QT, and QT corrected according to Fridericia's formula [QTcF]) as well as any rhythm abnormalities will be recorded. ECGs will be performed after the participant has been resting in a supine position for at least 5 minutes. ECG may be repeated once for confirmatory purposes if initial values obtained exceed the limits specified.

When ECG measurements coincide with safety and efficacy assessments, vital signs assessment or blood draws, procedures should be carried out in the following order: vital signs, TETRAS, ECG, blood sample collection for [redacted] clinical laboratory assessments, and questionnaires.

12.1.6. Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected at the visits and timepoints specified in Table 2. Analytes to be evaluated are summarized in Table 5.

Table 5: Summary of Clinical Laboratory Analytes

Biochemistry	*Renal Panel*: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate *Hepatic Panel*: albumin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, total protein, lactate dehydrogenase, gamma glutamyl transferase, creatine kinase (MB and MM) *Other*: Full lipid profile/panel, creatine phosphokinase, thyroid stimulating hormone, alcohol level, HbA1c
Coagulation	activated partial thromboplastin time, prothrombin time, and international normalized ratio
Hematology	red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell count with differential, platelet count, and if RBC indices are abnormal, reflex RBC morphology is indicated
Urinalysis	protein, glucose, pH, blood, leukocytes, leukocyte esterase, urobilinogen, bilirubin, ketones, nitrite, myoglobin

Note: Myoglobin (urinalysis) and serum creatine kinase (biochemistry) at Screening and at other timepoints at the discretion of the investigator. HbA1c will be collected at Screening and EOS/ETV Visit only.

12.1.6.1. Drugs of Abuse and Alcohol

A urine sample will be collected for assessment of selected drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, and opiates).

A serum sample will be collected for assessment of blood alcohol level.

12.1.6.2. Pregnancy Screen

A serum pregnancy test will be conducted for all female participants at Screening (Table 2); a urine pregnancy test will be conducted for all participants of childbearing potential at all other scheduled timepoints.

[redacted]

12.1.10. COVID-19 Questions

Information regarding diagnosis, isolation, and/or hospitalization due to coronavirus disease 2019 (COVID-19) will be documented at the time points indicated in the Schedule of Assessments (Table 2) and will be repeated as appropriate if a participant reports a COVID-19 diagnosis during the study. The site will be allowed to follow procedures already in place for screening participants for prior potential COVID-19 exposure. As a result, additional questions may be asked of the participant.

Questions to be asked are as follows:

26. Were you diagnosed with COVID-19 by a healthcare professional?
    - If the answer is “no”, no further questions.
    - If the answer is “yes”, the following questions are asked:
        - Did you have a test? If yes, was the result positive, negative, or inconclusive?
        - Were you isolated? If yes, what were the dates of isolation?
        - Were you hospitalized? If yes, what were the dates of hospitalization?
27. Did you receive the COVID-19 vaccine?
    - If the answer is “no”, no further questions.
    - If the answer is “yes”, the following questions are asked:
        - What is the reported name of the COVID-19 vaccine you received?
        - Who is the manufacturer of the COVID-19 vaccine you received?
        - On what date(s) did you receive the COVID-19 vaccine?

12.2. Adverse 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 pre-existing 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 study.

Laboratory abnormalities and changes from baseline in vital signs and ECGs 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 and changes from baseline in vital signs and ECGs 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 informed consent 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 patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.2. Serious Adverse Event 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. 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

12.2.4. Definition of Urgent Safety Measure and Unanticipated Problem

In accordance with Article 10(b) of Directive 2001/20/EC, some reported events may result in an urgent safety measure (USM), defined as an action that the sponsor and investigator may take in

order to protect the participants of a study against any immediate hazard to their health or safety. Examples of USMs include:

- Suspension of enrollment due to significantly higher incidence of death at one site
- Additional clinical or non-clinical investigations performed due to increased frequency of AEs
- Halting a clinical study for safety reasons

In accordance with FDA Guidance 21 Code of Federal Regulations Part 312.66, some reported events may qualify as an unanticipated problem (UP), defined as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (i) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (ii) the characteristics of the population being studied; related or possibly related to an individual's participation in the study; and
- Suggests the study may place the participant or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the study than was previously known or recognized.

Any UP must be reported within 24 hours of awareness via email to Sage and designee upon discovery due to the urgent reporting requirements to regulators and IRB(s)/IECs(s).

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 and 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 and designee.

Additional follow-up information, if required or available, should all be sent to Sage and 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 and 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 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. IRBs will be notified of SAEs and/or SUSARs as required by local law.

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 Sage and designee 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 and designee within 24 hours of

awareness. 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, pre-eclampsia) 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. Special Considerations

Drug abuse is the persistent or sporadic, intentional excessive use of IP which is accompanied by harmful physical or psychological effects in the participant. If an event of drug abuse occurs during the study, it must be reported to the sponsor and designee (see Table 1) using the Special Considerations Form within 24 hours of the site becoming aware of the event(s). If the drug abuse results in an AE or SAE, the AE or SAE must also be recorded and reported as described in Section 12.2.5 and Section 12.2.6, respectively.

Drug misuse refers to situations where IP is intentionally and inappropriately used not in accordance with the intended use as specified in the protocol. If an event of drug misuse occurs during the study, it must be reported to the sponsor and designee using the Special Considerations Form within 24 hours of the site becoming aware of the event(s). If the drug misuse results in an AE or SAE, the AE or SAE must also be recorded and reported as described in Section 12.2.5 and Section 12.2.6, respectively.

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 CRF; however, all overdoses must be recorded on the Special Considerations Form and sent to Sage and designee within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Sage and designee even if the overdose does not result in an AE. If an overdose results in an AE or SAE, the AE or SAE must also be recorded and reported as described in Section 12.2.5 and Section 12.2.6, respectively.

A medication error is any preventable event that may cause or lead to inappropriate medication use or participant harm while the medication is in the control of the healthcare professional, participant, or consumer. All medication errors must be recorded on the Special considerations form and sent to the sponsor and designee within 24 hours of the site becoming aware of the medication error. The medication error must be reported to the sponsor and/or designee even if the medication error does not result in an AE. If a medication error results in an AE or SAE, the AE or SAE must also be recorded and reported as described in Section 12.2.5 and Section 12.2.6, respectively.

13. STATISTICS

A 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/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 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 total TETRAS Performance Subscale Item 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.

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. Sensitivity analyses will be conducted by imputing missing data to evaluate the treatment effect.

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. All summaries will be provided by treatment group.

For the purpose of all primary and secondary 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, quartile, 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 frequency 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 by stratum (monotherapy cohort and adjunct therapy cohort) using the Safety Population.

Medical history will be listed by participant.

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

13.5. Efficacy Analysis

The estimand for the primary and secondary efficacy endpoint is defined as follows:

1. There are 4 treatment groups for the monotherapy participants to be evaluated: SAGE-324 (15 mg, 30 mg, 60 mg) and placebo.
2. The target population consists of the monotherapy participants ages 18 to 80 years and have a diagnosis of ET with combined total upper limb TETRAS Performance Subscale Item 4 of at least 12 with the dominant upper limb score of at least 6 and baseline TETRAS ADL score of at least 20.
3. The outcome for the primary efficacy endpoint is the change from baseline in TETRAS Performance Subscale Item 4 score on Day 91.
4. The population-level summary measure is the dose-response of different doses of SAGE-324 and placebo for the monotherapy cohort.
5. The treatment/hypothetical policy strategy will be adopted for the primary and secondary endpoint. For data collected after the intercurrent events, such as rescue medication, the treatment policy strategy will be used. For data not available after the intercurrent events, like premature discontinuation of study treatment, the hypothetical policy strategy will be adopted. This means that the dose-responses of different dose groups will be analyzed using all observed on-study data, regardless of the occurrence of the intercurrent event, including use of additional medication, premature discontinuation of treatment for any reason, or other protocol violations.

This will first be analyzed using a mixed-effects model for repeated measures (MMRM); the model will include treatment, baseline TETRAS Performance Subscale Item 4 upper limb tremor score, assessment timepoint, timepoint-by-baseline TETRAS Performance Subscale Item 4 upper limb tremor score 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. An unstructured covariance structure will be used to model the within-participant errors. If there is a convergence issue with the unstructured covariance model, Toeplitz 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.

After the MMRM analysis by PROC MIXED, the estimated mean and covariance matrix will be passed to the Multiple Comparisons and Modeling (MCP-Mod) analysis to test the dose-response relationship. In the analysis, multiple dose-response candidate models will be prespecified. The actual dose-response relationship will be assessed using the estimated means and covariance matrix from MMRM analysis. A critical value will be determined from the joint multivariate normal distribution of the contrast test statistics at the overall one-sided alpha level of 0.05. If the test statistic exceeds this critical value, a nonflat dose-response relationship will be demonstrated.

Secondary efficacy endpoints will be analyzed similarly to the primary endpoint.

13.6. Safety Analyses

Safety and tolerability of SAGE-324 will be evaluated by stratum (monotherapy cohort and adjunct therapy cohort) and overall using incidence of TEAEs/SAEs [redacted] and changes from baseline in vital signs, 12-lead ECGs[redacted]. [redacted] Safety data will also be listed by participant using the Safety Set.

13.6.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities Version 23.1 or higher. A 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 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.

13.6.2. Clinical Laboratory Evaluations

Results of clinical laboratory parameters in each scheduled visit and mean changes from baseline will be summarized in standard units. Normal ranges for each parameter will be provided by the laboratory; shift from baseline to postbaseline values in abnormality of results will be provided. Potentially clinically significant values will be summarized by treatment. Clinical laboratory results will be listed by participant and timing of collection.

13.6.3. Physical Examinations

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

13.6.4. Vital Signs

Vital sign results at each visit and mean changes from baseline will be summarized by scheduled visit. Potentially clinically significant values will be summarized by treatment. Vital sign results will be listed by participant and timing of collection.

13.6.5. 12-Lead Electrocardiogram

The following ECG parameters will be listed for ECGs for each participant: heart rate, PR, QRS, QT, and QTcF. ECG data will be summarized by visit. Potentially clinically significant values of QTcF will be summarized by treatment. ECG findings will be listed by participant and visit.

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 September 2015, or later.

All medications taken within 30 days prior to signing the 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. All medications taken at any time prior to signing the informed consent through the duration of the study for ET will also 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 planned sample size is 160 participants, randomized in a 1:1:1:1 ratio to each of the dose group (placebo and SAGE-324: 15 mg, 30 mg, and 60 mg), stratified by baseline propranolol use, with at least 104 (65%, 26 participants per dose group) monotherapy participants and up to 56 (35%, 14 participants per dose group) adjunct therapy participants.

The sample size of 104 participants for the monotherapy cohort assumes a change from baseline at Day 91 in TETRAS upper limb Item 4 score for the placebo group of -1.2 points, a maximum decrease of -3.2 points from Baseline for a dose response in the 15-60-mg dose groups with a standard deviation of 2.5. Under these assumptions with a few prespecified candidate dose-response models, including linear, loglinear, quadratic, exponential, logistic, Emax, sigEmax, and beta as shown in Figure 3, a sample size of 22 evaluable participants per group would provide 80% power for demonstrating a nonflat dose-response relationship by MCP-Mod approach, using a 1-sided type I error rate of 0.05. Assuming a nonevaluable rate of 15% across all treatment groups, approximately 104 participants (26 per treatment group) will be

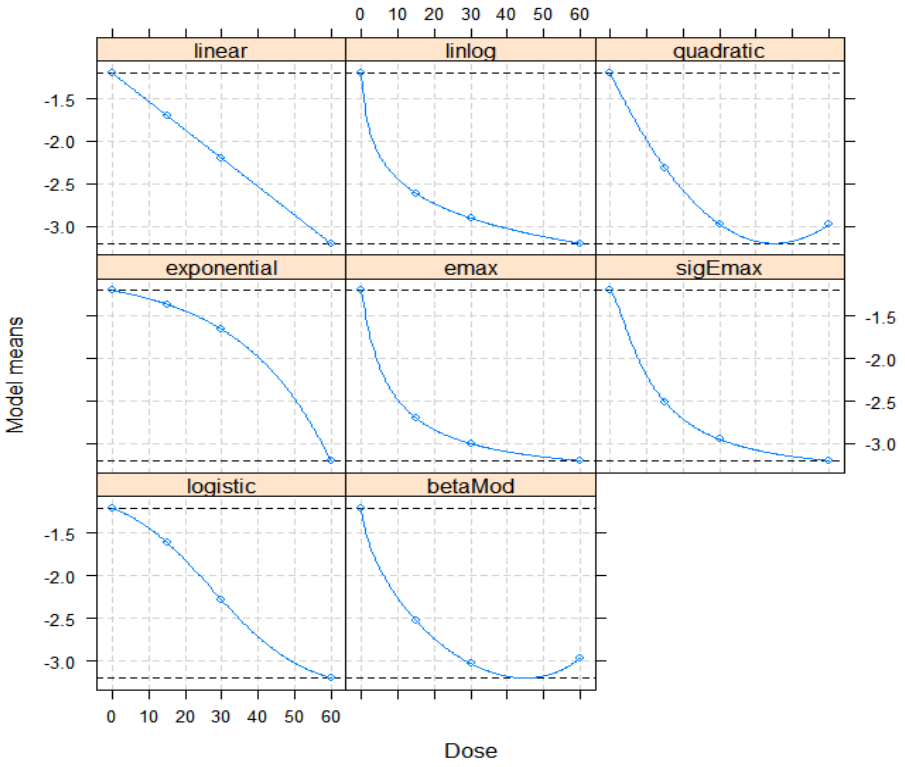
randomized. Additional participants may be enrolled if the overall nonevaluable rate is higher than 20%.

The sample size for adjunct therapy cohort is not based on statistical significance, but clinical considerations. Up to 56 adjunct therapy participants (14 per dose group) are to provide some adjunct therapy directional data on both efficacy and safety measures.

A blinded interim look at the primary and secondary endpoint data may be conducted to evaluate the sample size assumptions.

Additional participants may be randomized if the variances are larger than the assumptions above. However, no more than 200 participants, including adjunct therapy participants, will be randomized.

Figure 3: Prespecified Dose-response Models



13.8.1. Interim and Data Monitoring Committee Analyses

A blinded interim look at the primary and secondary endpoint data may be conducted to evaluate the sample size assumptions.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Unless otherwise waived or addressed in another forum (eg, investigator meeting), before an investigational site can enter a participant into the study, a representative of Sage will visit the investigational study site to:

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

During the study, a monitor from Sage 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 eCRFs, and that IP accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRF 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, medical records, source documents, 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 IEC.

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 IRB/IEC 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, Good Clinical Practice (GCP)/International Council for Harmonisation (ICH) guidelines, and any applicable regulatory requirements. The investigator should contact Sage Therapeutics immediately if contacted by a regulatory agency or IRB/IEC about an inspection.

14.3. Institutional Review Board or Independent Ethics Committee

The principal investigator must obtain IRB (or IEC) approval for the clinical study prior to enrolling a participant. Initial IRB (or IEC) approval, and all materials approved by the IRB (or IEC) 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 GCP 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. Protocol deviations that harm or increase the possibility of harm to the rights and welfare of a participant or a deviation made without prior IRB/IEC approval to eliminate an immediate hazard to the participant should be reported to the IRB/IEC per the IRB/IEC's written procedures.

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

The investigator must maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study 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/IEC, as appropriate. The investigator must obtain and document approval before he or she can enroll any participant into the study. The IRB/IEC must supply to the sponsor a list of the IRB/IEC membership and a statement to confirm that the IRB is organized and operates according to GCP and applicable laws and regulations.

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

The principal investigator is also responsible for providing the IRB/IEC 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/IEC according to local regulations and guidelines. In addition, the principal investigator must inform the IRB/IEC and sponsor of any changes significantly affecting the conduct of the study 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 study 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 study, 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 documentation. 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.

The ICF will include a provision stating that the participant may be contacted during or after the study with a request to participate in a related, follow-up research study in which they will be asked to provide responses to various questions regarding their experience in the Phase 2 study.

Throughout the study 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.

16.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data (including but not limited to, retained biological samples, images and/or recordings) will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Sage Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Sage Therapeutics or its representative(s) will be allowed to conduct visits at the investigation site and/or supporting 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 medical records 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 IP. 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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Signature Page for VV-CLIN-003085 v1.0

eSignature Approval Task	[redacted] 07-Nov-2023 15:21:24 GMT+0000

eSignature Approval Task	[redacted] 07-Nov-2023 15:24:31 GMT+0000

eSignature Approval Task	[redacted] 07-Nov-2023 15:38:48 GMT+0000

eSignature Approval Task	[redacted] 08-Nov-2023 13:44:42 GMT+0000

eSignature Approval Task	[redacted] 08-Nov-2023 15:20:32 GMT+0000

eSignature Approval Task	[redacted] 08-Nov-2023 16:08:51 GMT+0000

eSignature Approval Task	[redacted] 08-Nov-2023 20:36:04 GMT+0000

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Protocol 324-ETD-202, Amendment 5

Summary of Changes

Date of Amendment: 02 November 2023

A Phase 2 Double-Blind, Randomized, Placebo-Controlled, Dose-Response Study of SAGE-324 for the Treatment of Essential Tremor

Protocol Amendment 5 reflects the following changes:

- The Sponsor Contact has changed from:

[redacted]
Phone: [redacted]
E-mail: [redacted]

to:

[redacted]
Phone: [redacted]
Email: [redacted]

- The Sponsor Medical Monitor and Study Physician have changed from:

[redacted] MD, MSc
[redacted]
Phone: [redacted]
E-mail: [redacted]

to:

[redacted] MD
[redacted]
Phone: [redacted]
Email: [redacted]

- Section 9.2.2 Prohibited Medications: As per Administrative Letter #7 dated July 17, 2023, the following was added for clarity:
  - Any estrogen-containing products that are widely absorbed into the systemic circulation (eg, oral, transdermal, transvaginal, etc.), used for any indication, are prohibited from Day -14 and during the study.
- Section 2 Synopsis, Section 7.1 Overall Study Design, and Section 9.2.3 Other Restrictions:
  - Updated guidance regarding gaining experience with how the study drug may affect the participant before engaging in potentially hazardous activities requiring mental alertness, such as driving.

- Section 12.4 Overdose was changed to Section 12.4 Special Considerations, with new language for “abuse” and “misuse” to align with the Regulation (EU) No 536/2014 Of the European Parliament and Of The Council.
- Section 13.1 Data Analysis Sets and Section 2.2 Synopsis, the definition of the Full Analysis Set was updated to include participants enrolled under Version 1 of the protocol (dated 03 September 2021), who previously participated in a SAGE-324 study.
- The Sponsor Approval page was deleted to align with current Sage process and template.
- Minor formatting changes

Protocol 324-ETD-202, Amendment 4

Date of Amendment: 10 January 2023

A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, DOSE-RESPONSE STUDY OF SAGE-324 FOR THE TREATMENT OF ESSENTIAL TREMOR

Rationale for Protocol Amendment

The purpose for this protocol amendment is to update eligibility criteria and statistical analyses to include participants who are receiving propranolol for the treatment of essential tremor (ET).

Changes to the protocol include:

- Update objectives and endpoints to include monotherapy cohort (SAGE-324), adjunct therapy cohort (SAGE-324 + propranolol), and overall population (Synopsis and Section 6)
- Update sample size, stratification, and other statistical analyses to include monotherapy cohort and adjunct therapy cohort (Synopsis, Schedule of Assessments footnotes, Section 7.1, Section 7.2, Section 7.3, Section 8.4.4, Section 9.5, Section 13.4, Section 13.5, Section 13.6, and Section 13.8)
- Include additional 14 days (total of 42 days) in the Screening Period for sufficient time to taper ET medications other than propranolol after approval from the sponsor (Synopsis, Figure 1, and Section 7.1)
- Include information that participants in the adjunct therapy cohort must be on stable dose of propranolol (maximum total daily propranolol dose up to 320 mg allowed) for the treatment of ET from 3 months prior to screening through Day 90 of the study and that no additional propranolol as needed (PRN) is allowed (Inclusion criterion 8 [Synopsis and Section 8.1] and Section 9.2.2.1)
- Clarify that, a participant is to be excluded if receiving propranolol treatment for a medical condition other than ET (Exclusion criterion 9 [Synopsis and Section 8.2] and Section 9.2.2.1)
- Correction to the volume of distilled spirits (Inclusion criterion 9 [Synopsis and Section 8.1] and Section 9.2.3.
- Prohibit use of Cala Trio bracelet for treatment of ET from 2 weeks prior to Day 1 through Day 97 (Exclusion criterion 4 [Synopsis and Section 8.2] and Section 9.2.3)
- Clarify that prohibited use of botulinum toxin is for treatment of ET (Exclusion criterion 5 [Synopsis and Section 8.2])
- Include statement that there is currently no evidence of drug-drug interactions for SAGE-324 except for those outlined in the inclusion/exclusion criteria (Section 5.2)
- Clarify process for participant enrollment in a SAGE-324 long-term open label study (Synopsis, Section 7.1, and Section 9.3)

- Include nicotine products and alcohol use as part of medical history and monitoring during the study (Schedule of Assessments and Section 12.1.1)

Updates to organization, formatting, terminology, and Sage personnel have also been made.

Protocol 324-ETD-202, Amendment 3

Date of Amendment: 04 May 2022

A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, DOSE-RESPONSE STUDY OF SAGE-324 FOR THE TREATMENT OF ESSENTIAL TREMOR

Rationale for Protocol Amendment

The main purpose for this protocol amendment is to update eligibility criteria.

Changes to the protocol include:

- Permit alcohol consumption with restrictions on amount and timing with scheduled study visits (Inclusion Criterion 9 [Synopsis and Section 8.1] and Section 9.2.3)
- Permit current use of nicotine products at prestudy levels (new Inclusion Criterion 13 [Synopsis and Section 8.1] and Section 9.2.3)
- Exclude participants with nicotine use disorder (Exclusion Criterion 11 [Synopsis and Section 8.2] and Section 9.2.3)
- Remove alcohol and cotinine screening (Table 2 Schedule of Assessments and Section 12.1.6.1)
- Clarify that use of tremorgenic drug is prohibited within 14 days or 5 half-lives (whichever is longer) prior to Day 1 and that the use of established treatments with tremorgenic drugs is permitted if they do not cause or exacerbate tremors (Exclusion Criterion 2 and Section 9.2.2)
- Include creatine kinase, myoglobin, and HgA1c in clinical laboratory assessments (Table 2 and Section 12.1.6)
- Clarify that participants should not engage in potentially hazardous activities requiring mental activities until any sleepiness and sedative effects of IP have dissipated (Synopsis and Section 7.1)
- Prohibit use of estrogen-containing contraceptives that are widely absorbed into the circulatory system as an acceptable forms of highly effective contraception methods for participants of childbearing potential or for partners of male participants who are of childbearing potential (Section 9.2.4)
- Update safety reporting requirements (Table 1, Section 12.2.4, Section 12.2.6, Section 12.3, and Section 12.4)

Updates to organization, formatting, descriptions of procedures, and Sage personnel have also been made.

Protocol 324-ETD-202, Amendment 2

Date of Amendment: 04 May 2022

A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, DOSE-RESPONSE STUDY OF SAGE-324 FOR THE TREATMENT OF ESSENTIAL TREMOR

Rationale for Protocol Amendment

The main purpose for this protocol amendment is to remove [redacted] from the protocol.

Additional changes to the protocol include:

- [redacted]
- Update end of study information to include the opportunity to participate in a SAGE-324 long-term open-label safety study
- Clarify in exclusion criterion 12 that participants will not have known allergy to SAGE-324 because the study does not currently allow participants to have prior exposure to SAGE-324
- Clarify that prior essential tremor medications may be restarted following Day 97 of the study
- Harmonize treatment groups to include placebo throughout document

Updates to organization, formatting, and Sage personnel have also been made.

Protocol 324-ETD-202, Amendment 1

Date of Amendment: 04 March 2022

A PHASE 2, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, DOSE-RESPONSE STUDY OF SAGE-324 FOR THE TREATMENT OF ESSENTIAL TREMOR

Rationale for Protocol Amendment

The purpose for this protocol amendment is to update and clarify the protocol regarding the following:

- Clarify eligibility requirements with minor textual changes to inclusion criteria 3, 6, and 7 and exclusion criteria 1, 6, and 11 and addition of a new exclusion criterion 25
- Update Table 2 Schedule of Assessments as follows:
  - In table: update dispensing of IP to include Day 71 Visit
  - Footnote (d) for ECGs: delete triplicate sampling to harmonize with Section 12.1.5
  - [redacted]
  - [redacted]
  - Footnote (h): split footnote g in original version into new footnotes g and h to clarify importance of washout of prestudy essential tremor drugs prior to first TETRAS assessment
  - [redacted]
- [redacted]
- Clarify importance of prestudy essential tremor medication washout in Section 9.2.2 by addition of subsection header before existing text (new Section 9.2.2.1)
- Update end of study activities to include an offer to all participants for enrollment to a SAGE-324 long-term open-label study (Section 9.3)
- Update descriptions of efficacy assessments
- Update ECG assessment from triplicate to single readings at all timepoints (Section 12.1.5)
- Clarify procedures and assessments throughout the protocol with minor textual changes
- Update personnel for Sponsor Contact and Sponsor Medical Monitor/Study Sage Physician

A new section (Section 12.2.4) describing reporting procedures for Urgent Safety Measures and Unanticipated Problems has been added in response to regulatory feedback.

Updates and corrections to organization, terminology, punctuation, grammar, abbreviations, and formatting have also been made.