Official Title: AN OPEN-LABEL STUDY OF THE LONG-TERM SAFETY AND TOLERABILITY OF SAGE-324 IN PARTICIPANTS WITH ESSENTIAL TREMOR

NCT ID: NCT05366751

Document Date: Protocol Version 4.0: 08 November 2023

1. PROTOCOL OR AMENDMENT

Version Number	Date	Title
4.0	**02 November 2023**	AN OPEN-LABEL STUDY OF THE LONG-TERM SAFETY AND TOLERABILITY OF SAGE-324 IN PARTICIPANTS WITH ESSENTIAL TREMOR
3.0	**16 November 2022**	
2.0	**28 June 2022**	
1.0	**08 December 2021**	

Summary of Changes Version 4.0, 02 November 2023

Summary of Changes Version 3.0, 16 November 2022

Summary of Changes Version 2.0, 28 June 2022

AN OPEN-LABEL STUDY OF THE LONG-TERM SAFETY AND TOLERABILITY OF SAGE-324 IN PARTICIPANTS WITH ESSENTIAL TREMOR

PROTOCOL NUMBER: 324-ETD-303

IND NUMBER: 144989

Investigational Product	SAGE-324 Oral Tablet
Clinical Phase	Phase 2/3
Sponsor	Sage Therapeutics, Inc. 215 First Street Cambridge, MA 02142
Sponsor Contact	[redacted] Phone: [redacted] e-mail: [redacted]
Sponsor Medical Monitor	[redacted] MD [redacted] Phone: [redacted] Email: [redacted]
Date of Original Protocol	08 December 2021
Date of Amendment 1	28 June 2022
Date of Amendment 2	16 November 2022
Date of Amendment 3	02 November 2023

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INVESTIGATOR'S AGREEMENT

I have received and read the SAGE-324 Investigator's Brochure. I have read the 324-ETD-303 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date (DD/MMM/YYYY)

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Sage Study Physician	[redacted] MD [redacted]	Phone: [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 [redacted]	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:
An Open-label Study of the Long-term Safety and Tolerability of SAGE-324 in Participants with Essential Tremor

Number of Sites and Study Location: This study will take place at approximately 50 sites in the United States (US)

Phase of Development: 2/3

Planned Duration for Each Study Participant:
The duration of participation (from Screening through the final Follow-up Visit) for each participant will be until marketing authorization, projected to be up to approximately 5 years.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the long-term safety and tolerability of SAGE-324	• Incidence of treatment-emergent adverse events (TEAEs)
Secondary	
• To assess the long-term effect of SAGE-324 on other safety parameters	• Change from baseline in vital signs, electrocardiogram (ECG), clinical laboratory parameters, Epworth Sleepiness Scale (ESS), and Columbia-Suicide Severity Rating Scale (C-SSRS) responses • Physician Withdrawal Checklist (PWC-20) scores

[redacted]

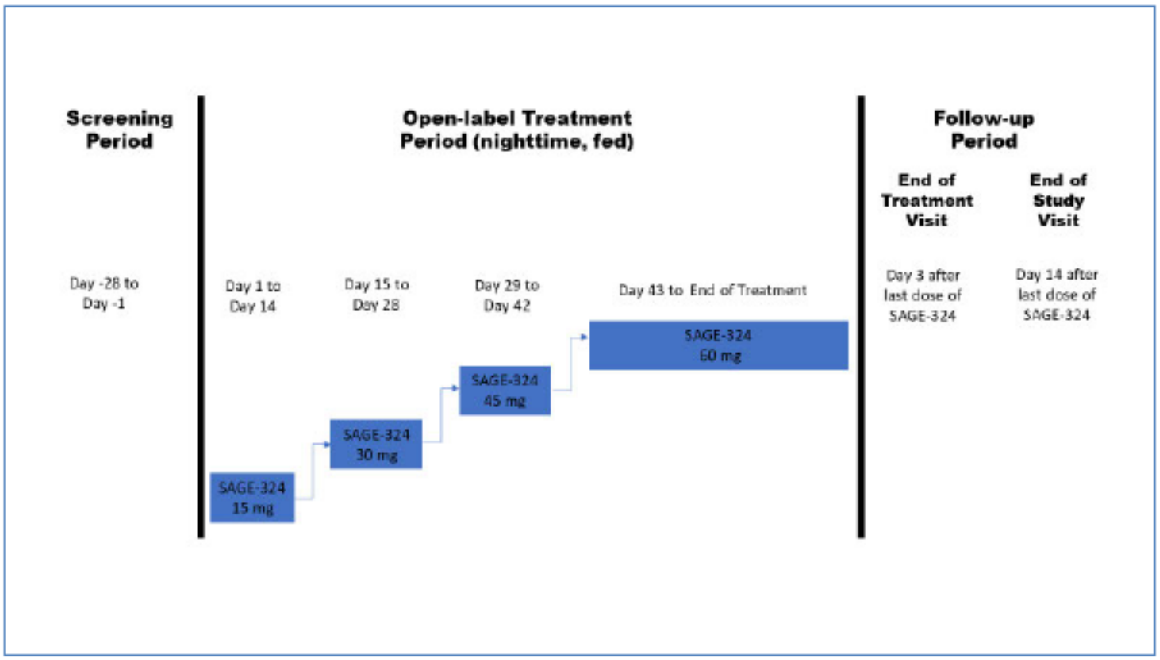
[redacted]

Study Description:

This is an open-label study to evaluate the long-term safety and tolerability of SAGE-324 in participants with essential tremor (ET) who have completed the planned End of Treatment (EOT) Visit and who were not early terminated during the planned Treatment Period in another SAGE-324 study.

The study design is presented in Figure 1.

Figure 1: Study Design



This study includes a Screening Period of up to 28 days, a Treatment Period with weekly outpatient visits for the first 8 weeks, outpatient visits on Weeks 10, 12, 16, 20, and 24, and quarterly outpatient visits thereafter to the end of dosing, and a 14-day Follow-up Period. After providing informed consent, participants will undergo screening assessments as outlined in Table 2 to determine eligibility.

[redacted]

Screening Period:

The Screening Period begins with the signing of the informed consent form (ICF). Eligible participants will complete additional eligibility and baseline assessments, as specified in the Schedule of Assessments (Table 2).

At the discretion of the investigator, clinical laboratory assessments from a completed SAGE-324 study may be used to determine eligibility for this study if taken within 28 days of Day 1.

Open-label Treatment Period:

Starting on Day 1, participants will self-administer on an outpatient basis a single dose of SAGE-324 once daily in the evening 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 safety, tolerability [redacted] as specified in Table 2, Table 3, and Table 4. In addition, safety phone call study visits will be conducted 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 and/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.

The Treatment Period will continue for as long as the participant continues to self-administer SAGE-324 or until marketing authorization, projected to be up to approximately 5 years.

Follow-Up Period:

Follow-up visits will be conducted on an outpatient basis when participants have completed the Treatment Period. Participants will continue to complete questionnaires as indicated in Table 4 and will return to the clinic 3 (±3) days after the last dose of SAGE-324 for safety, tolerability [redacted] at the End of Treatment (EOT) Visit. Participants will return to the study center for an End of Study (EOS) Visit 14 (±3) days after the last dose of SAGE-324.

Doses:

If a participant experiences adverse events (AEs) at any time during the Treatment Period that are considered by the investigator to be related to the investigational product (IP) and not tolerable, the investigator may reduce the dose of IP in 15 mg decrements, including during the initial dose escalation period. Administration of IP will be interrupted for 3 to 8 days before the initiation of the reduced dose.

Number of Participants (planned): It is estimated that approximately 750 participants will be dosed and complete the study to contribute exposures to the safety database for SAGE-324 in accordance with International Council for Harmonisation (ICH) E1a guidelines.

[redacted]

Eligibility Criteria:

Inclusion Criteria:

Participants are eligible to be included in the study if all of the following criteria are met:

1. Participant has signed an ICF before any study-specific procedures are 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) that may impact their ability to participate in the study, as determined by the investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.

4. Participant has a clinician-confirmed diagnosis of ET in compliance with all the following criteria:
   a. Duration of at least 3 years
   b. Absence of other neurological signs, such as dystonia, ataxia, parkinsonism, task- and position-specific tremors, sudden tremor onset, or evidence of stepwise deterioration of tremor
   c. Absence of historical or clinical evidence of tremor with psychogenic origin (including, but not limited to, eating disorders and major depression)
5. Participant has completed the planned End of Treatment (EOT) Visit and was not early terminated during the planned Treatment Period in another SAGE-324 study.
6. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.5 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), 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).
7. 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 9.2.5.
8. 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.
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 the EOS Visit.

   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 scheduled in-clinic study visits until all assessments have been completed.
10. Participant is willing to maintain prestudy consumption of products that contain nicotine starting at least 1 week prior to Day 1 and through EOS Visit.

Exclusion Criteria:

Participants are excluded from the study if any of the following criteria apply:

1. Participant has presence of alcohol withdrawal state.
2. Participant has had direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor.
3. Participant is taking and unable to discontinue the use of primidone at least 7 days prior to administration of the first dose of SAGE-324. [redacted]
4. Participant has a history (within 3 years of Screening) or ongoing oncologic disease, excluding skin cancers (squamous or basal cell carcinoma) for which treatment has been completed and any carcinoma in situ.

5. Participant has an ongoing clinically relevant medical or psychiatric condition that, in the judgment of the investigator, is not well managed and poses a risk for participation in the study.
6. Participant has history of substance dependence and/or abuse 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.
7. Participant has a known allergy to SAGE-324 or any excipient.
8. Female participant has a positive pregnancy test or confirmed pregnancy or is breastfeeding.
9. Participant has had exposure to another investigational drug or device within 30 days or 5 half-lives of the other investigational drug, whichever is longer, prior to the Day 1 visit and for the duration of the study.
10. Participant has a history of suicidal behavior within 2 years or answers "YES" to questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk of suicide in the opinion of the investigator.
11. Participant has night shift work.
12. Participant has any condition or comorbidity that in the opinion of the investigator would limit or interfere with the participant's ability to complete or partake in the study.
13. Participant is unwilling or unable to comply with study procedures and required training.
14. Participant has used any known moderate or strong cytochrome P450 3A4 inhibitors and/or inducers within 14 days or 5 half-lives (whichever is longer) prior to Day 1 or consumed grapefruit juice, grapefruit, Seville oranges, 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.
15. Participant is investigative site personnel or a member of their immediate families (spouse, parent, child, or sibling whether biological or legally adopted).

Investigational Product Dosage and Mode of Administration:

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

Participants will self-administer 15 mg SAGE-324 on Day 1 to Day 14, 30 mg on Day 15 to Day 28, 45 mg on Day 29 to Day 42, and then 60 mg daily starting on Day 43.

If a participant experiences AEs at any time during the Treatment Period that are considered by the investigator to be related to the IP and not tolerable, the investigator may reduce the dose of IP in 15 mg decrements, including during the initial dose escalation period. Administration of IP will be interrupted for 3 to 8 days before the initiation of the reduced dose.

Reference Therapy, Dosage and Mode of Administration:

Not applicable.

Duration of Treatment:

Each participant will receive SAGE-324 oral tablets from Day 1 to the EOT Period.

Statistical Methods:

A 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 safety, tolerability [redacted] 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 Safety Set will include all participants who are administered SAGE-324.

[redacted]

Determination of Sample Size

The planned sample size is approximately 750 participants to be enrolled and dosed to contribute exposures to the safety database for SAGE-324 in accordance with ICH E1A guidelines.

[redacted]

Safety Analysis

Safety and tolerability of study drug will be evaluated by incidence of TEAEs/serious adverse events and changes from baseline in vital signs, clinical laboratory evaluations, 12-lead ECG, and ESS. Suicidality will be analyzed based on the C-SSRS scores. Potential withdrawal symptoms will be analyzed based on PWC-20 scores.

[redacted]

Table 2: Schedule of Assessments: Screening to Treatment Period Day 57

Assessment	Screening	Treatment Period								
Study Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**
Window (Days)			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**
Informed consent	X									
Inclusion/Exclusion	X	X								
Demographics	X									
Medical history	X									
Pregnancy test	X (serum; all women)	X (urine; WOCBP only)				X (urine; WOCBP only)				X (urine; WOCBP only)
FSH (postmenopausal women only)	X									
Drug screen	X	X								
Complete physical examination, including neurological examination including MSE[a]	X									
Body height	X									
Body weight	X									
Vital signs[b]	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[c]	X	X						X		
Chemistry/hematology/ coagulation/urinalysis [d]	X	X	X	X		X		X		X
[redacted]										

Assessment	Screening	Treatment Period								
Study Day	**-28 to -1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**
Window (Days)			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**
C-SSRS ("Screening/Baseline" form)	X									
C-SSRS ("Since Last Visit" form)		X	X	X	X	X	X	X	X	X
[redacted]										
ESS	X	X	X	X	X	X	X	X	X	X
Participant training[g]	X	X								
Dispense SAGE-324[h]		X	X	X	X	X	X	X	X	X
SAGE-324 accountability			X	X	X	X	X	X	X	X
SAGE-324 administration[i]		Administered once daily before bed								
AEs/SAEs	X									
Prior medication and history[j]	X									
Concomitant medication	X	X								
Alcohol, nicotine products, and diet[k]	X									

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; ET = essential tremor; FSH = follicle stimulating hormone; ICF = informed consent form; IP = investigational product; MSE = mental state examination; [redacted] WOCBP = women of childbearing potential.

Note: The suggested order of assessments during clinic visits is vital signs, [redacted] ECG, blood sample collection for [redacted] clinical laboratory assessments, and questionnaires.

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

[b] 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., 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.

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

[d] Chemistry, hematology, coagulation, and urinalysis at Screening and at all additional timepoints. Myoglobin (urinalysis) and serum creatine kinase (biochemistry) at Screening and at additional timepoints at the discretion of the investigator. A serum sample for blood alcohol level will be collected at Screening and all additional timepoints. HbA1c will be collected at Screening.
At the discretion of the investigator, clinical laboratory assessments from another SAGE-324 study may be used to determine eligibility for this study if within 28 days of Day 1.

[g] Participants will be trained by study personnel on the use of software applications, IP diary, and devices necessary for the conduct of the study.

[h] Participants will self-administer orally 15 mg SAGE-324 on Day 1 to Day 14, 30 mg on Day 15 to Day 28, 45 mg on Day 29 to Day 42, and then 60 mg daily starting on Day 43. If a participant experiences AEs that are considered at any time in the Treatment Period by the investigator to be related to the IP and not tolerable, the investigator may reduce the dose of IP in 15 mg decrements, including during the initial dose escalation period. Self-administration of IP will be interrupted for 3 to 8 days before the initiation of the reduced dose.

[i] Participants will self-administer orally on an outpatient basis a single dose of SAGE-324 once daily in the evening before bed, with a snack if bedtime is not within 2 hours of the evening meal.

[j] Including all medications and supplements taken within the 30 days prior to signing the ICF through the first dose of SAGE-324, as well as a complete history of all treatments for ET since the year of diagnosis.

[k] Alcohol, nicotine use and diet will be collected to ensure compliance with IC#9, IC#10, and EC#14, respectively.

Table 3: Schedule of Assessments: Treatment Period Week 10 to Week 24

Assessment	Treatment Period				
Study Week	**10**	**12**	**16**	**20**	**24**
Window (Weeks)	**±1**	**±1**	**±1**	**±1**	**±1**
Pregnancy test	X (urine; WOCBP only)	X (urine; WOCBP only)	X (urine; WOCBP only)	X (urine; WOCBP only)	X (urine; WOCBP only)
Complete physical examination, including neurological examination including MSE[a]		X			X
Vital signs [b]	X	X	X	X	X
12-Lead ECG[c]		X			X
Chemistry/hematology/ coagulation/urinalysis[d]		X			X
[redacted]					
C-SSRS ("Since Last Visit" form)	X	X	X	X	X
[redacted]					
ESS	X	X	X	X	X
Dispense SAGE-324[f]	X	X	X	X	X
SAGE-324 accountability	X	X	X	X	X
SAGE-324 administration[g]	Administered once daily before bed				
AEs/SAEs	X				
Concomitant medication	X				

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ESS = Epworth Sleepiness Scale; IP = investigational product; MSE = mental state examination; [redacted] SAE = serious adverse event; [redacted]; WOCBP = women of childbearing potential.
Note: The suggested order of assessments during clinic visits is vital signs, [redacted] ECG, blood sample collection for [redacted] clinical laboratory assessments, and questionnaires.

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

[b] 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.

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

[d] Chemistry, hematology, coagulation, and urinalysis at Screening and at all additional timepoints. Myoglobin (urinalysis) and serum creatine kinase (biochemistry) at Screening and at additional timepoints at the discretion of the investigator. A serum sample for blood alcohol level will be collected at Screening and all additional timepoints. HgA1c will be collected at Week 12 and Week 24.

[redacted]

[f] If a participant experiences AEs at any time during the Treatment Period that are considered by the investigator to be related to the IP and not tolerable, the investigator may reduce the dose of IP in 15 mg decrements. Self-administration of IP will be interrupted for 3 to 8 days before the initiation of the reduced dose.

[g] Participants will self-administer on an outpatient basis a single dose of SAGE-324 once daily in the evening before bed, with a snack if bedtime is not within 2 hours of the evening meal.

Table 4: Schedule of Assessments: Month 9 to Follow-up Period

Assessment	Treatment Period						Follow-up Period	
Study Month	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 21**	**Month 24 to Month 60 (Every 3 Months)**	**EOT 3 (±3) days after last dose of SAGE-324**	**EOS 14 (±3) days after last dose of SAGE-324**
Window (Weeks)	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		
Pregnancy test	X (urine; WOCBP only)	X (urine; WOCBP only)	X (urine; WOCBP only)	X (urine; WOCBP only)	X (urine; WOCBP only)	X (urine; WOCBP only)	X (urine; WOCBP only)	X (urine; WOCBP only)
Complete physical examination, including neurological examination including MSE[a]	X	X	X	X	X	X	X	X
Body weight [b]		X				X		X
Vital signs [c]	X	X	X	X	X	X	X	X
12-Lead ECG[d]	X	X	X	X	X	X	X	X
Chemistry/hematology/ coagulation/urinalysis[e]	X	X	X	X	X	X	X	X
[redacted]								
C-SSRS ("Since Last Visit" form)	X	X	X	X	X	X	X	X
[redacted]								
ESS	X	X	X	X	X	X	X	X
PWC-20							X	X
Dispense SAGE-324[g]	X	X	X	X	X	X		

Assessment	Treatment Period						Follow-up Period	
Study Month	**Month 9**	**Month 12**	**Month 15**	**Month 18**	**Month 21**	**Month 24 to Month 60 (Every 3 Months)**	**EOT 3 (±3) days after last dose of SAGE-324**	**EOS 14 (±3) days after last dose of SAGE-324**
Window (Weeks)	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**		
SAGE-324 accountability	X	X	X	X	X	X	X	X
SAGE-324 administration [h]	Administered once daily before bed							
AEs/SAEs	X							
Concomitant medication	X							

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; IP = investigational product; MSE = mental state examination; [redacted] PWC-20 = 20-item Physician Withdrawal Checklist; SAE = serious adverse event; [redacted] WOCBP = women of childbearing potential.

Note: The suggested order of assessments during clinic visits is vital signs, [redacted] ECG, blood sample collection for [redacted] clinical laboratory assessments, and questionnaires.

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

[b] Weight assessed annually.

[c] 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.

[d] ECGs will be collected and read locally. 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 at Screening and at all additional timepoints. Myoglobin (urinalysis) and serum creatine kinase (biochemistry) at Screening and at additional timepoints at the discretion of the investigator. A serum sample for blood alcohol level will be collected at Screening and all additional timepoints. HbA1c will be collected at every other scheduled visit.

[redacted]

[g] If a participant experiences AEs at any time during the Treatment Period that are considered by the investigator to be related to the IP and not tolerable, the investigator may reduce the dose of IP in 15 mg decrements. Self-administration of IP will be interrupted for 3 to 8 days before the initiation of the reduced dose.

[h] Participants will self-administer on an outpatient basis a single dose of SAGE-324 once daily in the evening before bed, with a snack if bedtime is not within 2 hours of the evening meal.

[redacted]

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 6: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	adverse event
[redacted]	[redacted]
BMI	body mass index
CS	clinically significant
COVID-19	coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End of Study
EOT	End of Treatment
ESS	Epworth Sleepiness Scale
ET	essential tremor
$GABA_A$	γ-aminobutyric acid-gated chloride channel
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
NCS	not clinically significant
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PWC-20	20-item Physician Withdrawal Checklist
QTcF	QT corrected according to Fridericia's formula
SAP	statistical analysis plan
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Definition
TEAE	treatment-emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
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 noninherited cases may have toxin-based or other causality (Olanow 2008, Hopfner 2016). ET is the most common movement disorder in the US 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 tremors 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-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.

This open-label safety study is designed to collect long-term safety and tolerability data in participants with ET and will be initiated at the highest dose of SAGE-324 being assessed in the dose-ranging study 324-ETD-202.

5.1. Dose Justification

The present study (324-ETD-303) is a long-term, open-label study to evaluate the safety and tolerability of SAGE-324 in participants with ET. The dose selected for the study is the highest dose that is included in the dose-ranging study 324-ETD-202. Once the dose-ranging study is completed and a dose or doses are selected for inclusion in pivotal studies, this protocol will be amended to employ the highest of the doses included in the pivotal studies. This is in line with the ICH E1A guideline, requiring exposure at the dosage level(s) intended for clinical use.

In order to mitigate the adverse event (AE) of somnolence that was observed in study 324-ETD-201, nighttime dosing will be employed 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. Participants will be allowed to down-titrate at any time if intolerable AEs occur.

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.

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 in 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 Study 324-ETD-201, 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. There were 2 serious adverse events (SAEs) of mental status changes that were considered related to investigational product (IP) by the investigators. Some of the reported events required dose reduction or study discontinuation, but all events resolved without sequalae or requiring treatment.

In Study 324-ETD-201, participants were administered 60 mg SAGE-324 in the morning without prior up-titration. Participants in the current study will be dosed at nighttime and the dose will be titrated up to 60 mg in 15 mg steps in order 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 (as needed), or more frequently for AE monitoring as appropriate.

6. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the long-term safety and tolerability of SAGE-324	• Incidence of TEAEs
Secondary	
• To assess the long-term effect of SAGE-324 on other safety parameters	• Change from baseline in vital signs, electrocardiogram (ECG), and clinical laboratory parameters, Epworth Sleepiness Scale (ESS) and Columbia-Suicide Severity Rating Scale (C-SSRS) responses • Physician Withdrawal Checklist (PWC-20) scores

[redacted]

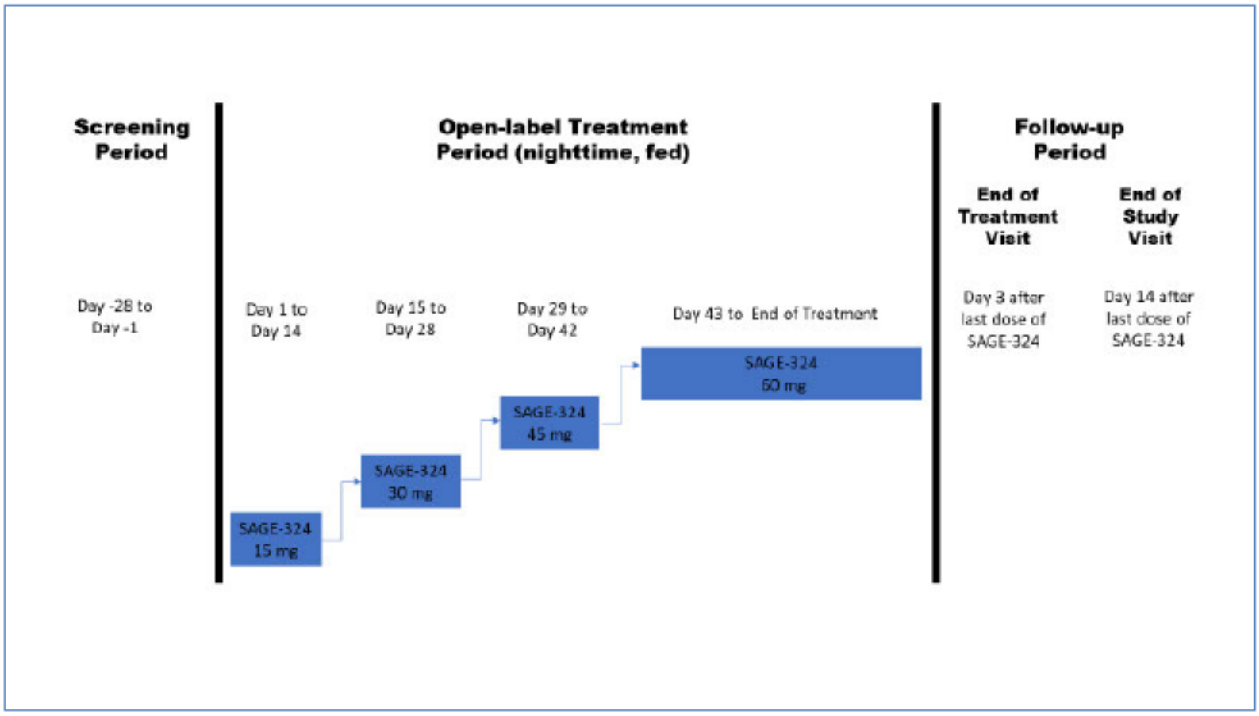
7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open-label study to evaluate the long-term safety and tolerability of SAGE-324 in participants with ET who have completed the planned End of Treatment (EOT) Visit and who were not early terminated during the planned Treatment Period in another SAGE-324 study.

The study design is presented in Figure 2.

Figure 2: Study Design



This study includes a Screening Period of up to 28 days, a Treatment Period with weekly outpatient visits for the first 8 weeks, outpatient visits on Weeks 10, 12, 16, 20, and 24, and quarterly outpatient visits thereafter to the end of dosing, and a 14-day Follow-up Period. After providing informed consent, participants will undergo screening assessments as outlined in Table 2 to determine eligibility.

[redacted]

Screening Period:

The Screening Period begins with the signing of the informed consent form (ICF). Eligible participants will complete additional eligibility and baseline assessments, as specified in the Schedule of Assessments (Table 2).

At the discretion of the investigator, clinical laboratory assessments from a completed SAGE-324 study may be used to determine eligibility for this study if taken within 28 days of Day 1.

Open-label Treatment Period:

Starting on Day 1, participants will self-administer on an outpatient basis a single dose of SAGE-324 once daily in the evening 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 safety, tolerability, [redacted] as specified in Table 2, Table 3, and Table 4. In addition, safety phone call study visits will be conducted 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 and/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.

The Treatment Period will continue for as long as the participant continues to self-administer SAGE-324 or until marketing authorization, projected to be up to approximately 5 years.

Follow-Up Period:

Follow-up visits will be conducted on an outpatient basis when participants have completed the Treatment Period. Participants will continue to complete questionnaires as indicated in Table 4 and will return to the clinic 3 (±3) days after the last dose of SAGE-324 for safety, tolerability, [redacted] at the End of Treatment (EOT) Visit. Participants will return to the study center for an End of Study (EOS) Visit, 14 (±3) days after the last dose of SAGE-324.

7.2. Number of Participants

It is estimated that approximately 750 participants will be dosed in and complete the study to contribute exposures to the safety database for SAGE-324 in accordance with International Council for Harmonisation (ICH) E1a guidelines.

[redacted]

7.3. Treatment Assignment

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

Participants will self-administer 15 mg SAGE-324 on Day 1 to Day 14, 30 mg on Day 15 to Day 28, 45 mg on Day 29 to Day 42, and then 60 mg daily starting on Day 43.

7.4. Dose Adjustment Criteria

If a participant experiences AEs at any time during the Treatment Period that are considered by the investigator to be related to the IP and not tolerable, the investigator may reduce the dose of

IP in 15 mg decrements, including during the initial dose escalation period. Administration of IP will be interrupted for 3 to 8 days before the initiation of the reduced dose.

7.5. Criteria for Study Termination

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to participants, or for administrative reasons. In the event of study termination, Sage Therapeutics will provide written notification to the investigator. Investigational sites must promptly notify their 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 concluded the study if he/she has completed dosing and completed the EOS Visit as per the Schedule of Assessments (Table 4) or is lost to follow-up.

8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

8.1. Participant Inclusion Criteria

Participants are eligible to be included in the study if all of the following criteria are met:

1. Participant has signed an ICF before any study-specific procedures are 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) that may impact their ability to participate in the study, as determined by the investigator, on physical examination, 12-lead ECG, or clinical laboratory tests.
4. Participant has a clinician-confirmed diagnosis of ET in compliance with all the following criteria:
   a. Duration of at least 3 years
   b. Absence of other neurological signs, such as dystonia, ataxia, parkinsonism, task- and position-specific tremors, sudden tremor onset, or evidence of stepwise deterioration of tremor
   c. Absence of historical or clinical evidence of tremor with psychogenic origin (including, but not limited to, eating disorders and major depression)
5. Participant has completed the planned End of Treatment (EOT) Visit and was not early terminated during the planned Treatment Period in another SAGE-324 study.
6. Female participant agrees to use at least one method of highly effective contraception as listed in Section 9.2.5 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), 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).
7. 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 9.2.5.
8. 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.

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 the EOS Visit.

   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 scheduled in-clinic study visits until all assessments have been completed.

10. Participant is willing to maintain prestudy consumption of products that contain nicotine starting at least 1 week prior to Day 1 and through EOS Visit.

8.2. Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Participant has presence of alcohol withdrawal state.
2. Participant has had direct or indirect injury or trauma to the nervous system within 3 months before the onset of tremor.
3. Participant is taking and unable to discontinue the use of primidone at least 7 days prior to administration of the first dose of SAGE-324. [redacted]
4. Participant has a history (within 3 years of Screening) or ongoing oncologic disease, excluding skin cancers (squamous or basal cell carcinoma) for which treatment has been completed and any carcinoma in situ.
5. Participant has an ongoing clinically relevant medical or psychiatric condition that, in the judgment of the investigator, is not well managed and poses a risk for participation in the study.
6. Participant has history of substance dependence and/or abuse prior to Screening, has a positive screen for drugs of abuse at Screening or predose on Day 1 (unless prescribed). Participants with nicotine use disorder that impacts their tremor are excluded.
7. Participant has a known allergy to SAGE-324 or any excipient.
8. Female participant has a positive pregnancy test or confirmed pregnancy or is breastfeeding.
9. Participant has had exposure to another investigational drug or device within 30 days or 5 half-lives of the other investigational drug, whichever is longer, prior to the Day 1 visit and for the duration of the study.
10. Participant has a history of suicidal behavior within 2 years or answers "YES" to questions 3, 4, or 5 on the C-SSRS at Screening or at Day 1 or is currently at risk of suicide in the opinion of the investigator.
11. Participant has night shift work.

12. Participant has any condition or comorbidity that in the opinion of the investigator would limit or interfere with the participant's ability to complete or partake in the study.
13. Participant is unwilling or unable to comply with study procedures and required training.
14. Participant has used any known moderate or strong cytochrome P450 3A4 inhibitors and/or inducers within 14 days or 5 half-lives (whichever is longer) prior to Day 1 or consumed grapefruit juice, grapefruit, Seville oranges, 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.
15. Participant is investigative site personnel or a member of their immediate families (spouse, parent, child, or sibling whether biological or legally adopted).

8.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but failed one or more eligibility criteria and are not subsequently enrolled in the study. A minimal set of screen failure information will be collected, including demography, screen failure details, eligibility criteria, and any SAE.

8.4. Investigational Product Discontinuation and End of Study Activities

8.4.1. Investigational Product Discontinuation

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

The reason for IP discontinuation and/or the reason for termination from the study must be documented in the participant's source documentation 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.

8.4.2. End of Study Activities

The duration of participation in this study is dictated by the duration of continued administration of IP. If the IP is permanently discontinued, two further study visits will be conducted: one approximately 3 days after IP discontinuation (EOT Visit) and another approximately 14 days after IP discontinuation (EOS Visit). If the participant does not attend the EOS Visit, they will be considered to be lost to follow-up.

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

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

8.4.3. Lost to Follow-up

A participant will be deemed lost to follow-up after 3 unsuccessful documented attempts to contact the participant.

[redacted]

9. TREATMENT OF PARTICIPANTS

9.1. Description of Investigational Product

SAGE-324 Tablet is an immediate release white to off-white, round, film-coated tablet containing 15 mg of SAGE-324 drug.

Participants will self-administer 15 mg SAGE-324 daily on Day 1 to Day 14. Each 15-mg dose will be self-administered as one 15-mg tablet per dose.

Participants will self-administer 30 mg SAGE-324 daily on Day 15 to Day 28. Each 30-mg dose will be two 15-mg tablets per dose.

Participants will self-administer 45 mg SAGE-324 daily on Day 29 to Day 42. Each 45-mg dose will be three 15-mg tablets per dose.

Participants will self-administer 60 mg SAGE-324 daily starting on Day 43. Each 60-mg dose will be four 15-mg tablets per dose.

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, as well as a complete history of all treatments for ET since the year of diagnosis.

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. If a prohibited medication is deemed necessary (Section 9.2.3), the participant should be discontinued from the study.

9.2.2. Use of Anti-tremor Medications

If applicable, and with the exception of primidone, participants must be on a stable dose of an anti-tremor medication for at least 5 half-lives prior to first dose of IP through the establishment of a stable dose of IP (approximately 4 weeks on same dose of IP). Thereafter, modifications to the anti-tremor medication are permitted.

In the case of primidone, the participant must stop taking primidone for at least 7 days before enrolling in the study. [redacted]

9.2.3. Prohibited Medications

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

- Participant is taking and unable to discontinue the use of primidone at least 7 days prior to administration of first dose of SAGE-324 and for the duration of dosing in the

study. [redacted]

- Participant has had exposure to another investigational drug or device within 30 days or 5 half-lives of the other investigational drug, whichever is longer, prior to the Day 1 visit.
- 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.
- 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) with the exception of primidone (7 days) prior to Day 1 and is unwilling to refrain from taking these medications for the duration of dosing. Use of mild cytochrome inhibitors and/or inducers may be permitted.

9.2.4. Other Restrictions

Participants must be willing to comply with all study procedures and restrictions, including the following for the time frames specified:

- Participant cannot have night shift work for the duration of dosing in the study.
- 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.
- Participant cannot have presence of alcohol withdrawal state.
- Participant cannot history of substance dependence and/or abuse prior to Screening and cannot have a positive screen for drugs of abuse at Screening or predose on Day 1.
- Participant cannot consume 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 foods for the duration of dosing.
- 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 the EOS Visit.

  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 scheduled in-clinic study visits until all assessments have been completed.

- Use of products that contain nicotine is maintained at prestudy levels starting at least 1 week prior to Day 1 and through The EOS Visit. Participants with nicotine use disorder that impacts their tremor are excluded.
- The use of medications other than fexofenadine for chronic allergies is recommended during participation in the study.

9.2.5. 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:

- Progesterone- 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 is prohibited.
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion or bilateral tubal ligation (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)
- 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) is also considered acceptable.

9.3. Intervention after the End of the Study

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

9.4. Treatment Adherence

Participants will be dispensed additional IP starting on Day 1 and at each clinic visit for use at home prior to the next clinic visit to orally self-administer at home with instructions specifying to 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 10.6.

Participants 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 an open-label study.

10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

10.1. Investigational Product

The SAGE-324 tablet is an immediate release white to off-white, round, film-coated tablet containing 15 mg of SAGE-324 drug substance. The tablet is composed of SAGE-324 drug substance [redacted] Opadry® II white is the coating agent.

10.2. Investigational Product Packaging and Labeling

SAGE-324 tablets are packaged in high density polyethylene containers. Drug product labels with all required information and conforming to all applicable Code of Federal Regulations and Good Manufacturing Practices/Good Clinical Practices (GCP) guidelines will be prepared by Sage Therapeutics.

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. No preparation is required for the tablet, which is administered orally as described below.

10.5. Investigational Product Administration

The participant will orally self-administer the IP 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. 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 enroll the eligible participant into the study and obtain the medication ID number for the IP to be dispensed to that participant. The medication ID number and the number of tablets dispensed must be recorded.

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

Participants who have previously been exposed to SAGE-324 will be separately identified in the safety database.

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.

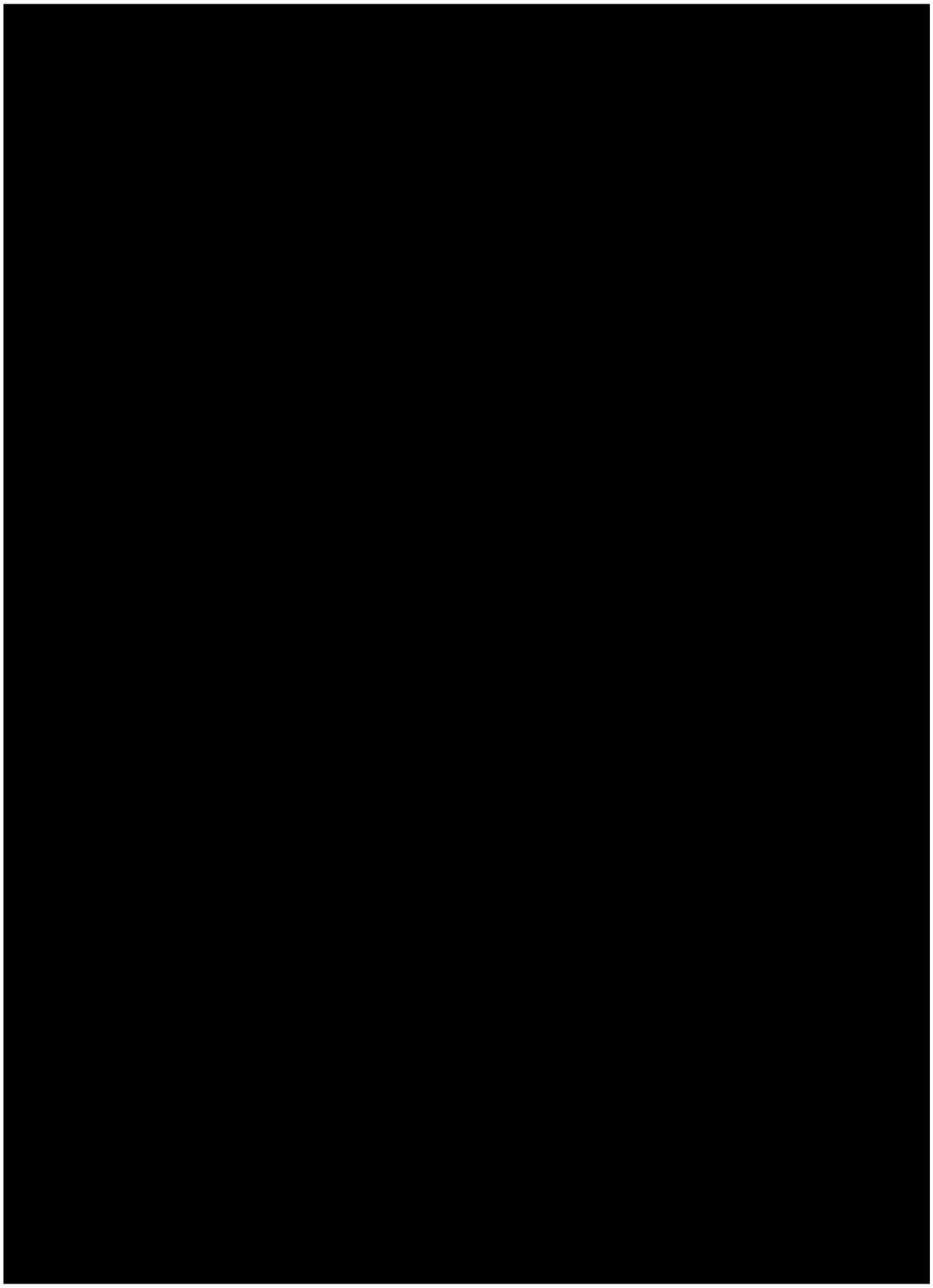
The investigator, pharmacist, or qualified designee is responsible for drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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).



12. SAFETY ASSESSMENTS

12.1. Safety Parameters

All assessments will be conducted according to the Schedules of Assessments (Table 2, Table 3, and Table 4).

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 (CS) or not clinically significant (NCS) in source documents.

12.1.1. Demography and Medical History

Demographic characteristics (age, race, sex, ethnicity) and a full medical history will be documented.

12.1.2. Weight and Height

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

12.1.3. Physical Examination

Complete physical examinations and a comprehensive neurological examination, including mental state examinations, should be performed at Screening, every 3 months during the Treatment Period, at the EOT Visit, at the EOS Visit, 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, 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.

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

12.1.5. Electrocardiogram

A 12-lead ECG will be performed according to the Schedules of Assessments (Table 2, Table 3, and Table 4). 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 collected and read locally.

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 assessments, vital signs assessment, or blood draws, procedures should be carried out in the following order: vital signs, ECG, blood draw.

12.1.6. Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected at the visits and time points specified on the Schedules of Assessments (Table 2, Table 3, and Table 4). Over the course of this study (5 years), the participant will have approximately 250 mL of blood drawn.

Analytes to be evaluated are summarized in Table 7.

Table 7: Summary of Clinical Laboratory Assessments

Biochemistry	*Renal Panel*: glucose, calcium, phosphorus, blood urea nitrogen, creatinine, sodium, potassium, chloride, total carbon dioxide content *Hepatic Panel*: albumin, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, total protein, lactate dehydrogenase, gamma glutamyl transferase, creatine kinase (MB and MM) *Other*: total lipid profile, creatine phosphokinase, thyroid stimulating hormone (TSH), 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, Week 12, Week 24, and at every visit every 3 months thereafter.

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

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

12.1.6.1. Drugs of Abuse and Alcohol

Separate urine samples for assessment of selected drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, tetrahydrocannabinol, methamphetamines, phencyclidine, and opiates) will be collected.

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

12.1.6.2. Pregnancy Test

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

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

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

The "Baseline/Screening" C-SSRS form will be completed at Screening (lifetime history and past 24 months). The "Since Last Visit" C-SSRS form will be completed at all subsequent time points outlined in the Schedules of Assessments (Table 2, Table 3, and Table 4).

12.1.8. Physician Withdrawal Checklist

The Physician Withdrawal Checklist (PWC) is based on the 35-item Penn Physician Withdrawal Checklist that was developed in the 1960s to measure benzodiazepine and benzodiazepine-like discontinuation symptoms. The PWC-20 is a shorter version of the Penn Physician Withdrawal Checklist based on the 20 items that provided the best differentiation from placebo in previous studies. The PWC-20 is made up of a list of 20 symptoms (eg, loss of appetite, nausea-vomiting, diarrhea, anxiety-nervousness, irritability) that are rated on a scale of 0 (not present) to 3 (severe) (Rickels 2008). The PWC-20 will be used to monitor for the presence of potential withdrawal symptoms after last dose of SAGE-324.

12.1.9. Epworth Sleepiness Scale

The ESS is a quick, 8-item, self-administered questionnaire where participants rate, on a 4-point scale (0 to 3), their usual chances of dozing off or falling asleep while engaged in 8 different activities. The total ESS score estimates the participant's average sleep propensity, across a range of activities in their daily lives (Johns 2002).

12.1.10. COVID-19 Procedures

The site should follow their internal plan, policies, and procedures for coronavirus disease 2019 (COVID-19).

The following information regarding diagnosis, isolation, and/or hospitalization due to COVID-19 will be documented as part of medical history, AE collection, and prior/concomitant medication/procedure collection at Screening and throughout the study.

Questions to be asked are as follows:

1. Were you diagnosed with COVID-19?
   - 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?
2. 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 participant 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 participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

12.2.2. Serious Adverse Event (SAE) Definition

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

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

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

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

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

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

12.2.3. 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

AE 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 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/IEC 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/IECs will be notified of SAEs and/or SUSARs as required by local law.

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 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 Safety Set will include all participants who are administered SAGE-324.

[redacted]

13.2. Handling of Missing Data

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

13.3. General Considerations

For the purpose of all safety, tolerability[redacted] 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.

13.4. Sample Size

The planned sample size is approximately 750 participants to be enrolled and dosed to contribute exposures to the safety database for SAGE-324 in accordance with ICH E1A guidelines.

[redacted]

13.5. Demographics and Baseline Characteristics

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

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

Medical history will be listed by participant.

[redacted]

[redacted]

13.7. Safety Analyses

Safety and tolerability of study drug will be evaluated by incidence of TEAEs/SAEs and changes from baseline in vital signs, clinical laboratory evaluations, 12-lead ECG, and ESS. Suicidality will be analyzed based on the C-SSRS scores. Potential withdrawal symptoms will be analyzed based on PWC-20 scores. Safety data will be listed by participant and summarized by dose group using the Safety Set.

13.7.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1or 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.

13.7.2. 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 post-baseline 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.

13.7.3. Physical Examinations

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

13.7.4. 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.

13.7.5. 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.

13.7.6. 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 informed consent through the duration of the study will be recorded. Those medications taken prior to the initiation of the start of IP will be denoted "Prior". Those medications taken prior to the initiation of the IP and continuing beyond the initiation of the IP or those medications started at the same time or after the initiation of the IP will be denoted "Concomitant".

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

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

13.7.7. Columbia Suicide Severity Rating Scale

Suicidality data collected on the C-SSRS at baseline and by visit during the Treatment Period will be listed and summarized for all participants. Listings will include behavior type and/or category for Suicidal Ideation and Suicidal Behavior of the C-SSRS.

13.7.8. Other Safety Analysis

Details for the analysis of ESS and PWC-20 will be provided in the SAP.

13.7.9. Interim and Data Monitoring Committee (DMC) Analyses

Not applicable.

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 screen a participant into the study, a representative of Sage or designee 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 Therapeutics 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 case report forms, 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 ethics committee.

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, GCP/ 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 (IRB) or Independent Ethics Committee (IEC)

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 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 or IEC as appropriate. The investigator must obtain and document approval before he or she can enroll any participant into the study. The IRB or IEC must supply to the sponsor a list of the IRB/IEC membership and a statement to confirm that the IRB/IEC is organized and operates according to GCP and applicable laws and regulations.

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

The principal investigator is also responsible for providing the IRB or 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 or 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, and 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.

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-003088 v1.0

eSignature Approval Task	[redacted] 07-Nov-2023 15:22:44 GMT+0000
eSignature Approval Task	[redacted] 07-Nov-2023 15:23:20 GMT+0000
eSignature Approval Task	[redacted] 07-Nov-2023 15:39:54 GMT+0000
eSignature Approval Task	[redacted] 08-Nov-2023 12:57:57 GMT+0000
eSignature Approval Task	[redacted] 08-Nov-2023 13:45:42 GMT+0000
eSignature Approval Task	[redacted] 08-Nov-2023 16:09:27 GMT+0000
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Protocol 324-ETD-303, Amendment 3

Summary of Changes

Date of Amendment: 02 November 2023

An Open-label Study of the Long-term Safety and Tolerability of SAGE-324 in Participants with Essential Tremor

Protocol Amendment 3 reflects the following changes:

- The Sponsor Contact has changed from:

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

to:

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

Note: As per Administrative Letter #6 dated September 25, 2023, the Sponsor Contact changed to [redacted]. In Protocol Amendment 3, the Sponsor Contact has been updated to [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 2 Schedule of Assessments: As per Administrative Letter #4 dated May 11, 2023, added collection of alcohol, nicotine products and diet to ensure alignment with Inclusion Criteria #9, #10, and Exclusion Criterion #14, respectively.
- Section 9.2.3 Prohibited Medications: As per Administrative Letter #5 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.
- The Sponsor Approval page was deleted to align with current Sage process and template.
- Minor formatting changes

Protocol 324-ETD-303, Amendment 2

Date of Amendment: 16 November 2022

AN OPEN-LABEL STUDY OF THE LONG-TERM SAFETY AND TOLERABILITY OF SAGE-324 IN PARTICIPANTS WITH 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 (new Inclusion Criterion 9 [Synopsis and Section 8.1] and Section 9.2.4)
- Permit current use of nicotine products at prestudy levels (new Inclusion Criterion 10 [Synopsis and Section 8.1] and Section 9.2.4)
- Exclude participants with nicotine use disorder (Exclusion Criterion 6 [Synopsis and Section 8.2] and Section 9.2.4)
- Remove alcohol and cotinine screening (Table 2 and Section 12.1.6.1)
- Clarify that participants have completed the planned End of Treatment Visit and were not early terminated during the planned Treatment Period in another SAGE-324 study (Inclusion Criterion 5 [Synopsis and Section 8.1] and study description [Synopsis and Section 7.1])
- Include creatine kinase, myoglobin, HgA1c, and blood alcohol level in clinical laboratory assessments (Schedules of Assessments 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 female participants of childbearing potential or for female partners of male participants who are of childbearing potential (Section 9.2.5)
- Define End of Study(EOS) (new Section 7.6)
- Define procedures for protection of participant data (new Section 16.4)
- Update safety reporting requirements (new Section 12.2.4, Section 12.3, Section 12.4, Section 15, and Section 16.4)

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

Protocol 324-ETD-303, Amendment 1

Date of Amendment: 28 June 2022

AN OPEN-LABEL STUDY OF THE LONG-TERM SAFETY AND TOLERABILITY OF SAGE-324 IN PARTICIPANTS WITH ESSENTIAL TREMOR

Rationale for Protocol Amendment

[redacted]

Additional changes to the protocol include:

- Update SAE reporting to include both CRO and Sage personnel following DSPV guidance (Table 1 and Section 12.2.5)
- Update ECG assessment from triplicate to single readings at all timepoints (Schedule of Events and Section 12.1.5)
- Add that, at the discretion of the investigator, clinical laboratory assessments from a completed SAGE-324 study may be used to determine eligibility for this study if taken within 28 days of Day 1 (Section 7.1)

[redacted]

- Update objectives (Section 6.0)
  - Update Primary objective to: "To evaluate the long-term safety and tolerability of SAGE-324"
  - Update Secondary safety objective to: "To evaluate the long-term effect of SAGE-324 on other safety parameters"

[redacted]

- Clarify eligibility requirements with minor textual changes to inclusion criterion 5 and exclusion criteria 3, 6, and 9 (Sections 8.1 and 8.2)
- Clarify that 20-item Physician's Withdrawal Checklist scores are not compared to baseline and that this assessment will be used to evaluate potential withdrawal symptoms (Section 13.7)
- Include use of breathalyzer for determination of alcohol use (Section 12.1.6.1)
- Clarify that participants that do not complete End of Study Visit will be considered lost to follow-up (Section 8.4.2)

Relevant changes in the protocol are also included in Section 2 (Synopsis).

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