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9. STATISTICAL METHODS INTERIM ANALYSIS PLAN

The following statistical analysis plan is provided:

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STATISTICAL ANALYSIS PLAN
METHODS
PROTOCOL NUMBER 324-ETD-303

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

Author(s) of SAP: [redacted]

Version: 1.0

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Sponsor:
Sage Therapeutics, Inc.
55 Cambridge Parkway
Cambridge, Massachusetts 02142

Authorization Signature Page

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

Author: [redacted]

23-Oct-2024 | 09:38 EDT

[redacted]
Date

Approved by: [redacted]

23-Oct-2024 | 11:23 EDT

[redacted] PhD
Date
[redacted]
Sage Therapeutics, Inc.

[redacted]
23-Oct-2024 | 09:54 EDT

[redacted] MD, MPH
Date
[redacted]
Sage Therapeutics, Inc.

[redacted]
23-Oct-2024 | 09:37 EDT

[redacted] MD
Date
[redacted]
Sage Therapeutics, Inc

[redacted]
24-Oct-2024 | 08:45 EDT

[redacted] PhD
Date
[redacted]
Sage Therapeutics, Inc

[redacted]
23-Oct-2024 | 21:11 EDT

[redacted] MPH
Date
[redacted]
Sage Therapeutics, Inc

[redacted]

23-Oct-2024 | 11:50 EDT

[redacted] PhD

Date

[redacted]

Sage Therapeutics, Inc

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1. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this statistical analysis plan (SAP).

Table 1: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	adverse event
[redacted]	[redacted]
BMI	body mass index
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
IP	investigational product
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
PWC-20	20-item Physician Withdrawal Checklist
QTcF	QT corrected according to Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
WHO-DD	World Health Organization Drug Dictionary

2. INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis of Study 324-ETD-303 and is based on the approved clinical study protocol dated 02 Nov 2023, Version 4.0.

This SAP addresses the objectives of the study and describes the planned statistical analyses and data presentations. All analyses and data presentations will be generated using SAS® Version 9.4 or higher software (SAS Institute, Cary, North Carolina, USA). This SAP will be finalized and approved before the clinical database lock. Any changes made to the SAP after the clinical database lock has occurred will be documented and discussed in the clinical study report for this study.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this study is to assess the long-term safety and tolerability of SAGE-324.

3.2. Secondary Objective

The secondary objective of this study is to assess the long-term effect of SAGE-324 on other safety parameters.

4. STUDY ENDPOINTS

4.1. Primary Endpoint

The primary endpoint of this study is the incidence of TEAEs.

4.2. Secondary Endpoints

The secondary endpoint(s) of this study are:

- The change from baseline in vital sign parameters
- The change from baseline in electrocardiogram (ECG) parameters
- The change from baseline in clinical laboratory parameters (eg, serum chemistry, hematology, coagulation, and urinalysis)
- Change from baseline in Epworth Sleepiness Scale (ESS) responses
- Physician Withdrawal Checklist (PWC-20) responses and total score
- Change from baseline in Columbia-Suicide Severity Rating Scale (C-SSRS) responses

[redacted]

5. STUDY DESIGN

5.1. Overall Design

This study is an open-label study to evaluate the long-term safety and tolerability of SAGE-324 in participants with Essetntial 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. 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. See the Schedule of Assessments (Appendix A) for the full list of study assessments and timings. The study is schematically presented in Figure 1.

[redacted]

Participants who have provided informed consent will undergo screening assessments up to 28 days prior to the planned day of dosing. Eligible participants will complete additional eligibility and baseline assessments.

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. The dosing will start at 15 mg, and according to the dose escalation schedule provided in Figure 1 below, will be escalated to 60 mg starting on Day 43. If a participant experiences adverse events (AE) 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.

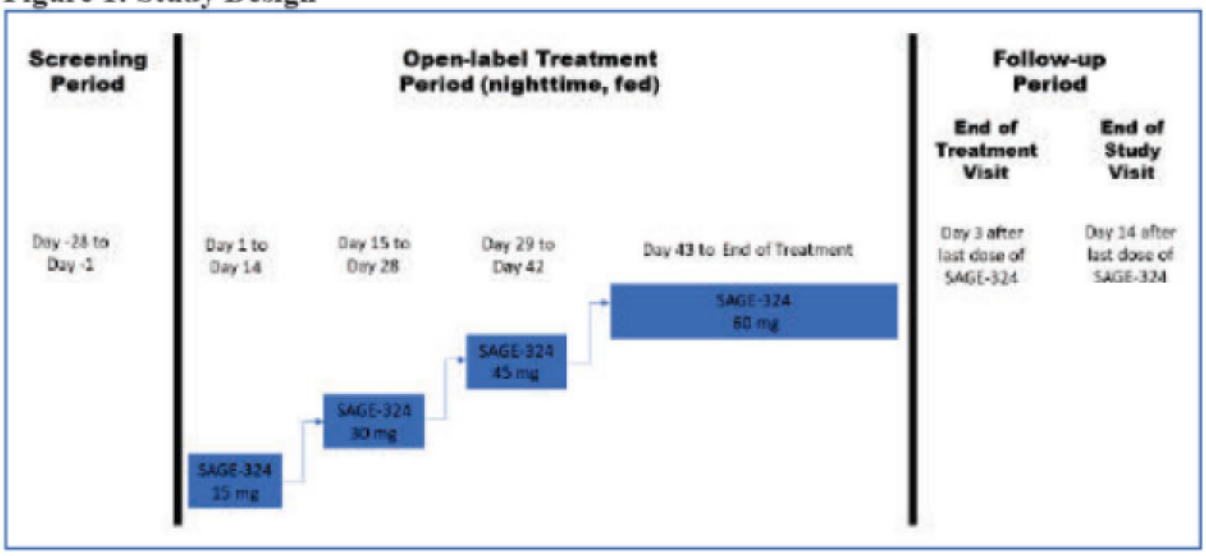
During the Treatment Period, participants will return to the study center for safety, tolerability[redacted]as specified in Appendix A. In addition, safety phone call study visits will be conducted as deemed appropriate by the investigator to review the current status of the participant. Participants will be trained in the use of software applications and devices necessary to complete questionnaires and/or self-rated study assessments.

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 visits will be conducted on an outpatient basis when participants have completed the Treatment Period. Participants will continue to complete questionnaires as indicated in Appendix A 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.

Figure 1: Study Design



5.2. Sample Size and Power

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

[redacted]

5.3. Randomization

This is an open label study, hence no randomization is applicable.

5.4. Blinding and Unblinding

This is an open label study, hence no blinding is applicable.

6. MODIFICATIONS

6.1. Modifications from the Approved Clinical Study Protocol

There are no modifications in analysis specified in the clinical study protocol (version 4.0, dated 02 Nov 2023).

6.2. Modifications from the Approved Statistical Analysis Plan

This is the first version of the SAP for the final analysis.

6.3. Modifications from the Approved DMC Charter

Not Applicable.

7. ANALYSIS SETS

7.1. All Participants Set

The All Participants Set will include all participants who have given written informed consent.

7.2. Safety Set

The Safety Set is defined as all participants who administered at least one dose of SAGE-324.

[redacted]

8. STATISTICAL ANALYSIS

8.1. General Considerations

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

For all safety [redacted] analyses where applicable, baseline is defined as the last non-missing measurement prior to the first dose of IP. For scores that are made up of item scores, all item scores must come from the same visit to be considered as baseline for the overall score.

Continuous endpoints will be summarized with n, mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), minimum (min), and maximum (max). The minimum and maximum will be reported with the same number of decimal places as the source (raw) data. Mean and median will be reported to 1 decimal place more than the source (raw) data and standard deviation will be reported to 2 decimal places more than the source (raw) data. Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision. In addition, change from baseline values will be calculated at each time point and summarized descriptively.

Categorical endpoints (eg, incidence of an adverse event) will be summarized using counts and percentages. Percentages will be presented to 1 decimal place unless otherwise specified.

Participants will be summarized according to treatment received. "By-visit" summaries are based on the last dose received before the specific evaluation. Adverse events summaries are based on the last dose received before the start of the AE. Note that it is possible for a participant to be counted under more than one dose in summaries. Since baseline is by definition before the first dose of IP, baseline values in listing will have no dose designation, and in summaries it will be presented under "Sage-324 Overall". For displays for which no such date applies, e.g. demographics, disease history, etc., the presentation will not be by dose group, but will be by aggregate SAGE-324 group.

8.2. Background Characteristics

8.2.1. Participant Disposition

The summary of disposition will use the All Participants Set and include number of participants who were screened, screen failed, successfully screened but did not dose, and successfully screened and dosed (overall and by previous study participation), and, using the number of participants who successfully screened and dosed as the denominator, the number and percentage of participants who completed treatment, who discontinued treatment (overall, by dose level, and by primary reason for discontinuing treatment), who completed the study, and who discontinued the study (overall and by primary reason).

If a participant is rescreened because he/she has been a screen failure the first time, the status of the participant will be determined from the second screening. In the count of screened participants, such a participant will be counted only once.

A completer of the study is a participant with the study completion question answered 'Yes' on the End of Study / Study Disposition CRF page. A completer of treatment is a participant with the treatment completion question answered 'Yes' on the IP Completion / Discontiuation CRF page. The primary reason for discontinuing the study is provided in the respective CRF page.

The number of participants in each of the analysis sets will also be summarized and presented, using the All Participants Set. The reasons for participants being excluded from each analysis set will be listed (using All Participants) but not summarized.

8.2.2. Protocol Deviations

Protocol deviations will be captured on eCRF and categorized by the study team as major and minor deviations. The major deviations will be summarized by type using the Safety Set. The minor deviations will be included in the listing but not summarized. The COVID-19 related protocol deviations will be summarized separately.

Inclusion/exclusion violations will be listed for All Participants (excluding screen failures) but not summarized.

8.2.3. Demographics and Baseline Characteristics

Demographic data (age, sex, race, and ethnicity), baseline characteristics (height, weight, BMI, dominant upper limb), [redacted] will be summarized with descriptive statistics using the Safety Set.

Baseline subgroups will be summarized for the following categories:

- Race (Black or African American, White, Asian, Other)
- Sex (Female, Male)
- Age (<65, 65 to 80 years)
- BMI (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2)
- [redacted]
- [redacted]

Listings will be provided for demographics, other baseline characteristics, and informed consent data.

8.2.4. Medical/Surgical History

Medical/surgical history will be coded to Medical Dictionary for Regulatory Activities (MedDRA) terms, using Version 25, or higher. The MedDRA version will be included in the footnotes of related outputs. Medical/surgical history will be summarized using discrete summary statistics for each MedDRA System Organ Class (SOC) and Preferred Term (PT) using the Safety Set.

Age at ET diagnosis (years), age participant thinks ET started (years), years with ET diagnosis (age at baseline minus age at ET diagnosis), years since participant thinks ET started (age at baseline minus age when participant thinks ET started), tremor responsive to alcohol, past treatments for ET, and response to past treatment for ET will be summarized using the Safety Set. The data listing will also include reason for discontinuation from the past treatment.

The disease history will be summarized for the following categories:

- Age at ET diagnosis (<40 years, 40 to 60 years, >60 years)
- Age participant thinks ET started (<20 years, 20 to 40 years, >40 to 60 years, >60 years)
- Years with ET diagnosis (3 to <6 years, 6 to 10 years, >10 years)
- Years since participant thinks ET started (3 to <6 years, 6 to 10 years, >10 years)
- Tremor responsive to alcohol: Yes (Intermediate, Worked Well), No (No, a little), NA
- Past treatment for ET (Yes, No)
- Response to past treatment for ET: Yes (Intermediate, Worked Well), No (No, a little), Yes and No (denominator for percentages will be participants having past treatment for ET)

8.2.5. Prior and Concomitant Medications

Medications will be recorded at each study visit and coded into drug class (anatomical therapeutic chemical [ATC] Level 2) and PT using World Health Organization-Drug dictionary (WHO-DD) Global B3 March 2022, or later.

All medications taken within 30 days prior to informed consent through the duration of the study (including start and end dates, route, dose/units, frequency, and indication) will be recorded on the electronic case report form (eCRF).

Those medications taken prior to the initiation of the 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". Note that medication taken before the initial dosing of IP and continued after the initial dosing will be categorized as a prior medication and separately as a concomitant medication.

Medications will be flagged in the listing according to whether they are "Prior" or "Concomitant" as defined above. In the event of a missing start or stop date associated with a medication, only the classification (prior and/or concomitant) will be imputed using the algorithm described in Appendix B. Dates will not be imputed.

Prior and concomitant medications will be summarized separately using the Safety Set as the number and percentage of participants with each medication at both the ATC and PT levels. Concomitant procedures will be listed with SOC/PT, but not summarized.

8.2.6. Investigational Product Exposure

Total investigational product exposure (in mg) is defined as the total mg of SAGE-324 that was taken during the study. If a participant skips a dose on any of the days, the dose taken is 0 mg.

Total exposure duration to SAGE-324 (in days) is defined as (date of last dose – date of first dose + 1). Note that this does not exclude days when the dose has been missed.

Planned exposure for participants with no unscheduled dose reductions/increases is defined as the sum of:

- 14 days of treatment (Day 1 through Day 14) times 15 mg
- 14 days of treatment (Day 15 through Day 28) times 30 mg
- 14 days of treatment (Day 29 through Day 42) times 45 mg
- Number of days from Day 43 to end of treatment, inclusive, times 60 mg

If a participant has an unscheduled dose reduction/increase, or dose reductions/increases, planned exposure will be as indicated until the point of the first unscheduled reduction/increase. Planned exposure from the point of the first unscheduled reduction/increase will be the assigned dose times the number of days from the date of the reduction/increase (inclusive) to the date of the next reduction/increase (exclusive) or the date of end of treatment (inclusive). Planned exposure for any additional unscheduled reductions/increases will be handled in a similar manner as the assigned dose times the number of days from the date of the reduction/increase (inclusive) to the date of the next reduction/increase (exclusive) or the date of end of treatment (inclusive).

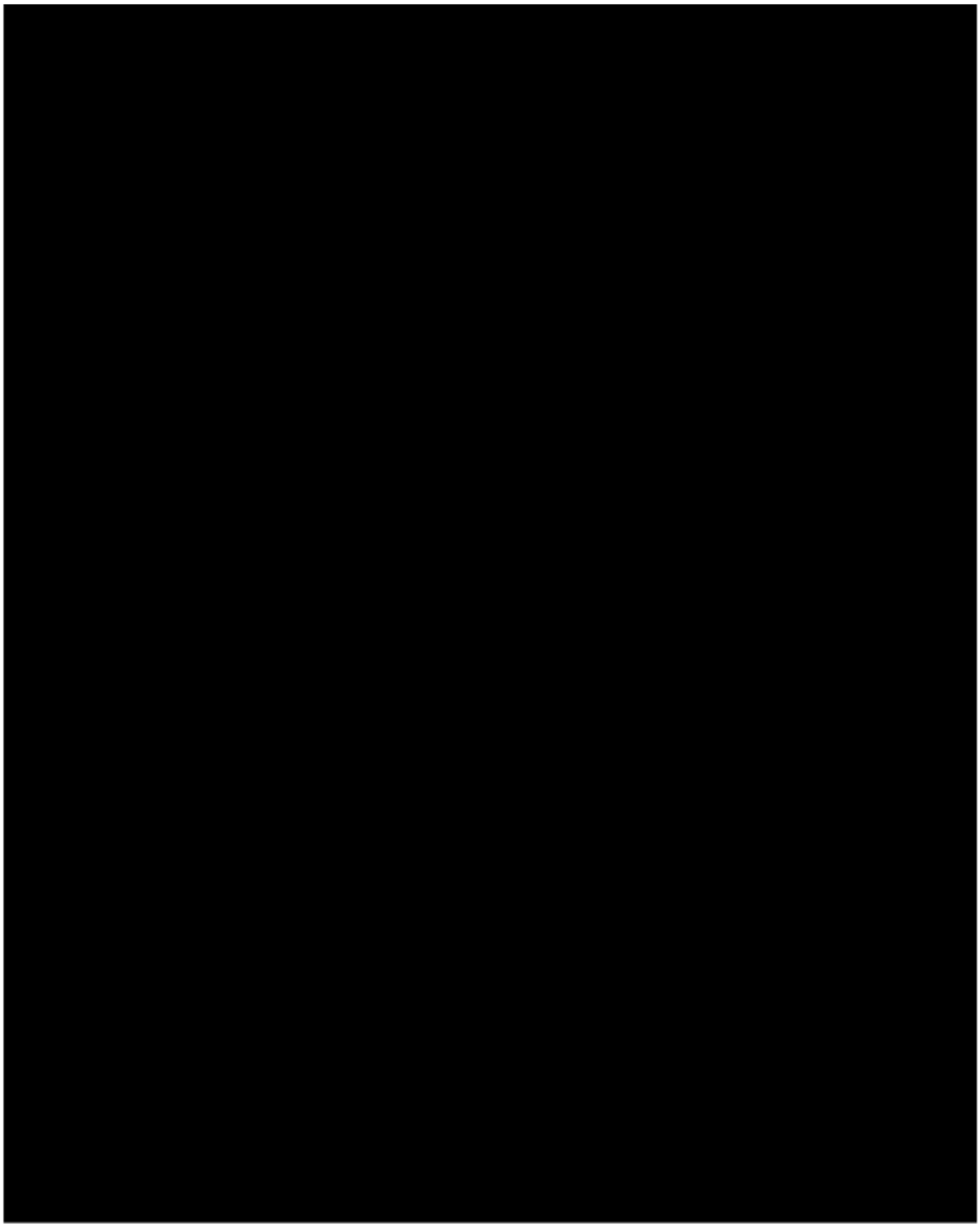
Percent of the planned exposure received is defined as the total investigational product exposure, divided by planned exposure, times 100.

Total investigational product exposure, total exposure duration, and percent of planned exposure received will be summarized using the Safety Set. The number and percentage of participants with percent of planned exposure received <80%, 80% to <100%, and ≥100% will be summarized. Total exposure duration (over all doses taken) will also be summarized by dose at time of treatment discontinuation using the Safety Set.

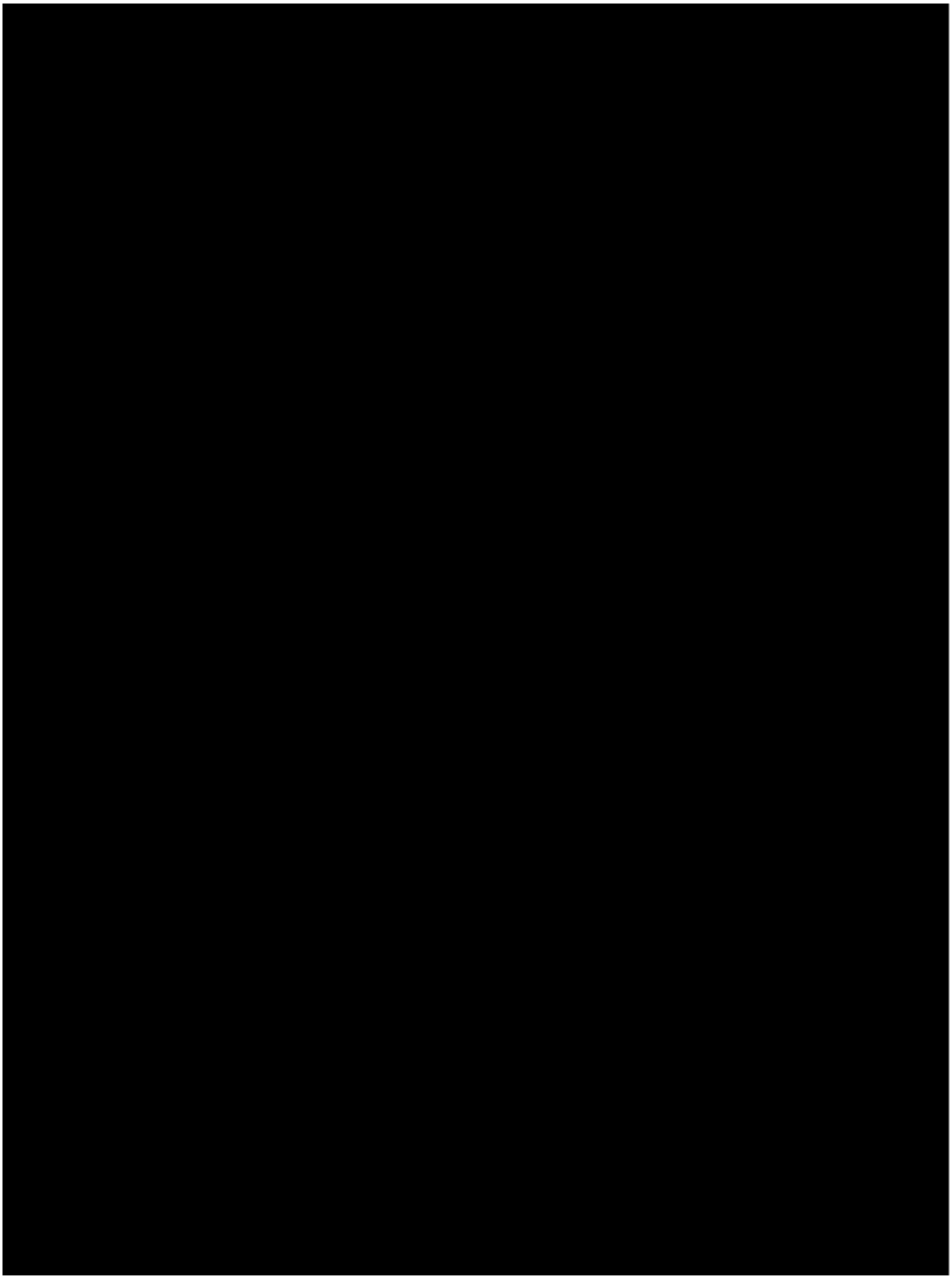
8.2.7. Investigational Product Adherence

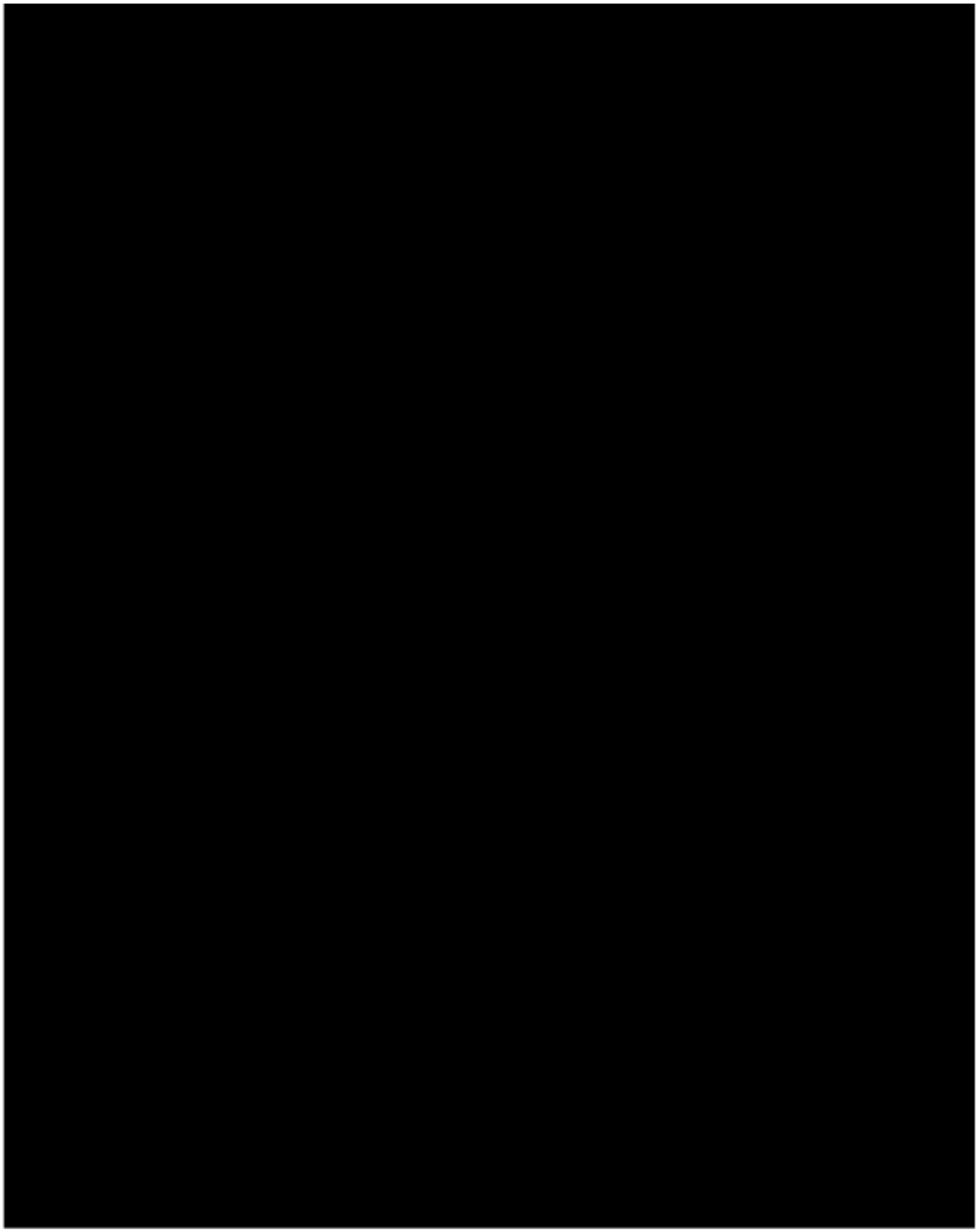
IP adherence (%) is defined as the number of tablets taken, divided by the number of tablets planned to be taken, times 100. Number of tablets planned to be taken will be derived using an algorithm identical to that used for the derivation of planned exposure, but with the assigned dose replaced with the number of assigned tablets (15 mg = 1 tablet per day, 30 mg = 2 tablets per day, 45 mg = 3 tablets per day, 60 mg = 4 tablets per day).

Total tablets taken and IP adherence will be summarized descriptively using the Safety Set. Number and percentage of participants with IP adherence in categories <75%, 75 to 100%, >100% will be provided.



[redacted]





8.4. Safety Analysis

Safety and tolerability of SAGE-324 will be assessed based on TEAEs, changes from baseline in clinical laboratory evaluations, 12-lead ECGs, and vital signs, C-SSRS, PWC-20, and ESS. Safety data will be listed by participant.

For safety summary tables, the safety endpoints evaluated at scheduled visits are taken as done and nominal visit will be summarized as scheduled visits. For multiple values from the specific visit window, the choice of the visit record will be following the same rule as described in Section 8.3.2.

All safety summaries will be prepared by dose level and overall for the Safety Set. See Table 4 for details on how safety endpoints will be presented.

Table 4: Presentation of Safety Endpoints

Safety Evaluation	Incidence	Raw Value	Change from Baseline	Abnormality	Derived PCS values
TEAEs	X	*			
Vital Signs		X, *	X		X, *
12-lead ECG		X, *	X	X, *	X, * (QTcF only)
Safety Labs (Chemistry, Hematology, Urinalysis)		X, *	X	X, *	X, *
ESS	X	*	X		
PWC-20	X	*			
C-SSRS	X	*	X		

X = Safety Assessment will be summarized in tables
* = Safety Assessment will be presented in individual participant data listings
Note: PCS = Potentially Clinically Significant.

8.4.1. Adverse Events

Adverse events will be coded using MedDRA Version 25 or higher. In the event of a missing/incomplete start or stop date associated with an adverse event, only the treatment-emergence will be imputed using the algorithm described in Appendix B. Dates will not be imputed.

A TEAE is defined as an AE with onset at or after the first dose of IP (SAGE-324). Summary tables of AEs will include TEAEs only and will summarize data using the Safety Set participants overall and by dose level taken immediately prior to the AE onset.

An overall adverse event summary table will be presented for TEAEs and will include the number and percent of participants experiencing at least one:

- TEAE
- Maximum severity of TEAE (mild TEAE, moderate TEAE, severe TEAE)

- TEAE leading to dose interruption
- TEAE leading to dose reduction
- TEAE related to IP
- TEAE leading to IP discontinuation
- TEAE leading to study discontinuation
- Serious TEAE
- Serious TEAE related to IP
- Serious TEAE leading to IP discontinuation
- Serious TEAE leading to study discontinuation
- TEAE resulting in death

The incidence of TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT). In addition, summaries will be provided by maximum severity (mild < moderate < severe) and by maximum relationship (related > not related) to IP. Any TEAEs leading to IP discontinuation, any TEAE leading to study discontinuation, and any treatment-emergent SAEs will also be summarized, sorted by descending frequency in SOC and PT.

Participants will be counted only once within each SOC and PT at the maximum severity in the following order: severe, moderate, and mild. Participants will be counted only once within each SOC and PT at the strongest relationship to IP in the following order: related, not related to IP. An AE with missing severity will be considered as 'severe', and with missing relationship to IP will be considered as 'related' for the purposes of summarizing these data.

The incidence of TEAEs and treatment-emergent SAEs will also be presented in order of decreasing frequency by PT.

All AEs (including those with onset before the start of IP) through the end of the study will be listed. In addition, separate listings containing individual participant AE data for all deaths, SAEs, AEs leading to IP discontinuation, and AEs leading to study discontinuation will be provided.

8.4.2. Clinical Laboratory

All statistical analyses of laboratory values will be performed using SI units. The following parameters are mentioned in the protocol, hence will be summarized; any other parameters for which data are reported will be listed but not summarized.

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

Some numeric lab values may be reported as '<n.n' or '>n.n'; these will be analyzed in the summary statistics as n.n/2 and n.n, respectively. For example, triglycerides recorded as "<0.50" mmol/L would be analyzed as 0.25 mmol/L and potassium recorded as ">6.0 mmol/L" would be analyzed as 6.0 mmol/L.

All by-visit laboratory summary tables will present results for the Safety Set participants overall, and by dose level received prior to the given evaluation. For summarization of incidence data any time post-baseline, participant data will be summarized according to the last dose received when a particular criterion was met (thus, a participant may contribute data under more than one dose if a criterion was met post-baseline while taking different doses).

Continuous hematology, chemistry, coagulation, and urinalysis results (raw and change from baseline) will be summarized at each scheduled time point. Categorical urinalysis results will be summarized by frequencies and percentages at each scheduled time point. The number and percentage of participants with shift from baseline based on the laboratory normal ranges provided by the laboratory will be tabulated at each scheduled visit.

Any laboratory value considered clinically significant by the investigator is captured as an adverse event.

The number and percentage of participants with potentially clinically significant (PCS) values at any time after IP administration (including unscheduled visits) will be summarized for the hematology, chemistry, and coagulation parameters defined in Table 5, Table 6, and Table 7, respectively. PCS values for each scheduled visit and end-of-treatment and end-of-study values will also be provided. These summaries will be done using the Safety Set, overall for SAGE-324 as well as by dose level.

Liver function tests will be monitored closely; PCS values (Table 8) will be summarized using the Safety Set for incidence any time post-baseline for these PCS thresholds (for conditions involving more than one parameter, the results need to be from the same timepoint).

Chemistry, hematology, coagulation, and urinalysis data will be listed with the values outside the normal ranges and PCS criterion flagged. Blood cell morphology and microscopy test results will be listed when available but not summarized. Virus serology, pregnancy tests, and urine drugs of abuse data will be listed but not summarized.

Table 5: Potentially Clinically Significant Values for Hematology

Laboratory Parameter	Sex	Units	Criteria for PCS Values (Observed values)	
			High	Low
Hemoglobin	Male	g/L	>185	<115
	Female	g/L	>170	<100
Hematocrit	Male	Fraction of 1	>0.55	<0.385
	Female	Fraction of 1	>0.49	<0.345
Platelet count		10^9/L	>600	<125
White blood cell		10^9/L	>15	<2.5
Basophils		10^9/L	>0.5	NA
Eosinophils		10^9/L	>1.5	NA
Neutrophils		10^9/L	NA	<1.5
Lymphocytes		10^9/L	>6.0	<0.5
Monocytes		10^9/L	>1.4	NA

Table 6: Potentially Clinically Significant Values for Chemistry

Laboratory Parameter	Units	Criteria for PCS Values (Observed values)	
		High	Low
Albumin	g/L	>70	<28
Blood urea nitrogen	mmol/L	>10.71	NA
Calcium	mmol/L	>2.75	<2.0
Chloride	mmol/L	>120	<90
Creatinine	mmol/L	>3xULN or >3x Baseline	
Gamma Glutamyl Transferase		>3xULN	
Glucose	mmol/L	>13.9	<2.8
Sodium	mmol/L	>150	<132
Potassium	mmol/L	>5.4	<3.3
Protein	g/L		<45
Bicarbonate	mmol/L	>34	<18
Chloride	mmol/L	>120	<90
Phosphorus	mmol/L	>1.94	<0.61
Liver Function Tests (LFT)			
Bilirubin	µmol/L	>2xULN	
Aspartate Aminotransferase	U/L	>3xULN	
Alanine Aminotransferase	U/L	>3xULN	
Alkaline Phosphatase	U/L	>1.5xULN	

Table 7: Potentially Clinically Significant Values for Coagulation

Parameter	Potentially Clinically Significant Values
Prothrombin time (PT)	>=1.11 x ULN
Activated partial thromboplastin time (aPTT)	>1.5 x ULN

Table 8: Potentially Clinically Significant Values for Liver Function Tests

Parameter	Potentially Clinically Significant Values
Alanine Aminotransferase	>3xULN, >5xULN, >10xULN
Aspartate Aminotransferase	>3xULN, >5xULN, >10xULN
Alanine Aminotransferase **OR** Aspartate Aminotransferase	>3xULN, >5xULN, >10xULN
Alkaline Phosphatase	>1.5xULN, >2xULN
Total Bilirubin	>1.5xULN, >2xULN
Total Bilirubin > 2xULN **AND** (Alanine Aminotransferase **OR** Aspartate Aminotransferase >3xULN), any time postbaseline, do not need to be at the same visit	
Potential Hy's Law: [Total Bilirubin >=2xULN **AND** Alkaline Phosphatase <2xULN, measured at the same visit] **AND** [(Alanine Aminotransferase **OR** Aspartate Aminotransferase >3xULN) AND Alkaline Phosphatase <2xULN, measured at the same visit], two conditions at any time postbaseline, do not need to be at the same visit	

8.4.3. Electrocardiogram

All by-visit ECG summary tables will present results for Safety Set participants overall, and also by dose level received prior to the evaluation. For summarization of incidence any time post-baseline, participant data will be summarized according to the last dose received when a particular criterion was met (thus, a participant may contribute data under more than one dose if a criterion was met post-baseline while taking different doses). Last value on treatment and last value on study will be summarized under the dose level last received.

The average of any multiple values collected at one visit will be used for summarization of continuous variables, including baseline ECG values. For each ECG measurement (heart rate and PR, QRS, QT, and QTcF intervals), the observed value at each scheduled visit and change from baseline at each scheduled visit will be provided. This summary will also include last values on treatment and on study. Last value on treatment is defined as the last post-baseline value between first dose of IP (exclusive) and up to last dose of IP + 1 day (inclusive). Last value on study is defined as the last post-baseline value after the first dose of IP.

In addition, the number and percentage of participants with PCS and potentially clinically significant change (PCSC) values will be summarized by scheduled timepoint and for any time post-baseline, including last value on treatment and last value on study. Individual values of QTcF will be used for PCS determination rather than the average of multiple values collected at one visit. Potentially clinically significant values will be identified for ECG parameters as outlined in Table 9.

A shift table of overall ECG interpretation from baseline to scheduled post-baseline visits will be presented for the following categories: 'Normal', 'Abnormal, Not Clinically Significant', and 'Abnormal, Clinically Significant'. The shift table will be presented by visit – overall and by dose level.

Clinically significant abnormal findings will be reported as adverse events. The average of any multiple values collected at one visit of each parameter will be included in the data listing.

Table 9: Potentially Clinically Significant Values for QTcF

Units	Criteria for PCS Values (Observed Values)		Criteria for PCSC Values (Change from Baseline)	
	High	**Low**	**Increase**	**Decrease**
msec	>450 msec and ≤480msec >480 msec and ≤500msec >500 msec	NA	>30 msec and ≤60 msec >60 msec	NA

8.4.4. Vital Signs

All by-visit vital sign summary tables will present results for Safety Set participants overall, and also by dose level received prior to the evaluation. For summarization of incidence at any time post-baseline, participant data will be summarized according to the last dose received when a particular criterion was met (thus, a participant may contribute data under more than one dose if a criterion was met post-baseline while taking different doses).

Vital sign results (systolic and diastolic blood pressure [mmHg], pulse pressure (mmHg), body temperature [°C], heart rate [beats per minute or bpm], and respiratory rate [breaths per minute]) and changes from baseline will be summarized by scheduled visit – overall and by dose level. Pulse pressure is defined as [systolic blood pressure - diastolic blood pressure].

Potentially clinically significant values will be identified for vital sign parameters as outlined in Table 10. For any post-baseline visit, potentially clinically significant values will be summarized by visit.

Any vital sign results considered clinically significant by the investigator will be captured as adverse events.

Table 10: Potentially Clinically Significant Values for Vital Sign Parameters

Vital Sign	Units	Criteria for PCS Values (Observed values)		Criteria for PCSC values (Change from Baseline values)	
		High	Low	Increase	Decrease
Heart rate (supine and standing)	Beats/min	>120	<40		
Systolic Blood Pressure (supine and standing)	mmHg	>180	<90	≥30	≥30
Diastolic Blood pressure (supine and standing)	mmHg	>110	<50	≥20	≥20
Supine - Standing Systolic Blood Pressure	mmHg	≥20			
Supine – Standing Diastolic Blood Pressure	mmHg	≥10			
Orthostatic hypotension: supine – standing SBP and DBP	mmHg	SBP ≥20 and DBP ≥10			
		SBP ≥20 or DBP ≥10			

8.4.5. Physical Examination

The occurrence of a physical examination and the date and time, along with the results of the mental status exam and the abbreviated neurological exam are collected. These will be presented in individual participant data listings only using the Safety Set. After screening, any clinically significant abnormal findings in physical examinations will be reported as AEs.

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

All by-visit C-SSRS summary tables will present results for Safety Set participants overall, and also by dose level received prior to the given visit. For summarization of incidence data any time post-baseline, Safety Set participant data will be summarized according to the dose received immediately prior to the evaluation (thus, a participant may contribute data under more than one dose if a criterion was met post-baseline while taking different doses).

Suicidality data collected on the C-SSRS is collected during the clinic visits at Screening and post-baseline visits. The C-SSRS includes 'yes' or 'no' responses for assessment of suicidal ideation with numeric rating for the severity (from 1 to 5 with 5 being the most severe) and behavior (from 6 to 10 with 10 being 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 visits.

The categorical outcomes of C-SSRS with binary response ("Yes"/ "No") include:

Suicidal ideation with 5 being the worst:

- 1: wish to be dead

- 2: non-specific active suicidal thoughts
- 3: active suicidal ideation with any methods (not plan) without intent to act
- 4: active suicidal ideation with some intent to act, without specific plan
- 5: active suicidal ideation with specific plan and intent

Suicidal behavior with 10 being the worst:

- 6: preparatory acts or behavior
- 7: aborted attempt
- 8: interrupted attempt
- 9: actual attempt
- 10: completed suicide

Suicidal behavior is considered worse than suicidal ideation. The participant's non-suicidal self-injurious behavior is also assessed separately as part of C-SSRS:

- 11: self-injurious behavior without suicidal intent

Baseline for each question is defined as the worst of the assessments done before the first dose of IP, excluding the lifetime version. This will typically include the 'past 24-month' version from screening and 'since last visit' version from Day 1, as well as any unscheduled visits done before the first dose of IP; any 'Yes' response will make the baseline value as 'Yes'.

The number and percentage of participants with at least one response of 'Yes' to any C-SSRS suicidal ideation or suicidal behavior item, as well as for participant's non-suicidal self-injurious behavior, will be summarized by visit.

Change from baseline for C-SSRS will be assessed using shift tables. Summary of shift from baseline in C-SSRS suicidal ideation and suicidal behavior will be presented for the categories "no suicidal ideation/behavior", "suicidal ideation", and "suicidal behavior" for each scheduled assessment time point. If the answer to all 5 assessments in suicidal ideation and all 5 assessments in suicidal behavior is 'No', then the category for the table is considered as 'No suicidal ideation/behavior'. If any of the assessments in suicidal behavior are 'Yes', the category is considered as 'Suicidal behavior'. If any of the assessments in suicidal ideation are 'Yes' but all assessments in suicidal behavior are 'No', the category is considered as 'Suicidal ideation'.

In addition, a summary of shift in suicidal ideation from baseline maximum rank score for any time post-baseline maximum rank score will be presented. Maximum score 0 refers to all 'No' for all assessments in the desired period for all 5 questions on suicidal ideation.

8.4.7. Physician Withdrawal Checklist (PWC-20)

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 trials. 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 syndrome following discontinuation of SAGE-324.

Summarization of PWC-20 data will be presented using the Safety Set – overall and by dose last received immediately prior to the evaluation. Descriptive statistics for the total PWC-20 score will be presented at End of Treatment (defined as the first available assessment after the last dose of study within 1 day of last dose) and End of Study. The change from End of Treatment to End of Study in PWC-20 total score will be provided. The number and percentage of participants with each PWC-20 item and reporting severe on a PWC-20 item will be presented at each visit. Descriptive statistics for the number of PWC-20 items and the number of severe PWC-20 items experienced at each visit will also be presented.

8.4.8. Epworth Sleepiness Scale (ESS)

The ESS is a quick, 8-item, self-administered questionnaire where participants rate, on a 4-point scale of 0 (no chance of dozing) to 3 (high chance of dozing), 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).

All by-visit ESS summary tables will present results using the Safety Set – overall, and also by dose last received immediately prior to the evaluation. Descriptive statistics for each of the 8 individual items (continuous and by categorical response) at each scheduled visit, the total ESS score at each scheduled visit, and change from baseline in the total ESS score at each postbaseline visits will be presented. The number and percentage of participants with a total ESS score of 0, no chance of dozing off, will also be presented at each visit.

8.4.9. Other Safety Analysis

Not applicable.

[redacted]

8.6. Other Analysis

Not applicable.

9. SUMMARY OF INTERIM AND DMC ANALYSES

9.1. Interim Analysis

Not applicable.

9.2. DMC Analysis

Not applicable.

10. REFERENCES

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11. LIST OF APPENDICES

APPENDIX A. 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] 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 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.

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.

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[f]	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.

APPENDIX B. HANDLING OF MISSING DATES

Partial dates will adhere to the following conventions in order to classify TEAEs and to classify prior and concomitant medications.

In general, listings will present the actual partial or missing values rather than the imputed values that may be used in derivation.

Adverse Events

In the event of a missing/incomplete start or stop date associated with an adverse event, only the treatment-emergence will be imputed using the algorithm below. Dates will not be imputed.

In general, if the missing/incomplete start date is not clearly prior to initiation of treatment, then the AE will be considered a TEAE.

If the AE end date is prior to the initiation of treatment, the AE will not be considered a TEAE.

If the AE end date is on or after the initiation of treatment:

- If the AE start date is completely missing or if the year is missing, then the AE will be considered a TEAE
- For partial AE start dates:
    - Known year, unknown month and day (or known year and day, unknown month)
        - If the year is the same as or later than the year of the first dose, the AE will be considered a TEAE
        - Otherwise, the AE will not be considered a TEAE
    - Known year and month, unknown day
        - If the month and year are the same as or later than the month and year of the first dose, the AE will be considered a TEAE
        - Otherwise, the AE will not be considerd a TEAE

Prior and Concomitant Medications

No imputation process will be used to estimate missing data, except for the purposes of classifying medications as prior and/or concomitant. The following algorithms will be used for partially missing dates.

For start dates of medication uses:

- The day and month are missing: if the participant started receiving the study dosing in the reported year, the first dosing date will be used as the start date; otherwise '01 January' will be used as the start date.

- The day is missing: if the participant started receiving the study dosing in the reported month and year, the first dosing date will be used as the start date; otherwise, the first day of the reported month and year will be used as the start date.

For stop dates of events or medication uses:

- The day and month are missing: if the study end date is in the reported year, the study end date will be used as the stop date; otherwise, '31 December' will be used as the stop date.
- The day is missing: if the study end date is in the reported month and year, the study end date will be used as the stop date; otherwise, the end of the reported month and year will be used as the stop date.

If a medication has the stop date completely missing or missing the year, this medication will be considered as ongoing and concomitant. If a participant is missing a treatment start date, medication will not be classified as either prior or concomitant.

APPENDIX C. LIST OF DISPLAYS

Display Number	Display Title	Analysis Set Used
Tables		
14.1.1	Disposition of Participants	All Participants
14.1.2	Analysis Sets	All Participants
14.1.3.1	Major Protocol Deviations	Safety Set
14.1.3.2	Protocol Deviations Related to COVID-19	Safety Set
14.1.4.1	Demographics and Baseline Characteristics	Safety Set
14.1.4.2	Demographics and Baseline Characteristics - Subgroups	Safety Set
14.1.5	Summary of Disease History	Safety Set
14.1.6	Medical/Surgical History	Safety Set
14.1.7.1	Prior Medications	Safety Set
14.1.7.2	Concomitant Medications	Safety Set
14.1.8.1	Investigational Product Exposure	Safety Set
14.1.8.2	Total Exposure Duration by Dose at Investigational Product Discontinuation	Safety Set
14.1.8.3	Investigational Product Adherence	Safety Set
[redacted]		

[redacted]

14.3.1.1	Summary of Treatment-Emergent Adverse Events	Safety Set
14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set
14.3.1.3	Treatment-Emergent Adverse Events by Preferred Term	Safety Set

14.3.1.4	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set
14.3.1.5	Treatment-Emergent Adverse Events Leading to Investigational Product Discontinuation by System Organ Class and Preferred Term	Safety Set
14.3.1.6	Treatment-Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term	Safety Set
14.3.1.7	Treatment-Emergent Adverse Events by Maximum Severity	Safety Set
14.3.1.8	Treatment-Emergent Adverse Events by Maximum Relationship to Investigational Product	Safety Set
14.3.1.9	Serious Treatment-Emergent Adverse Events by Preferred Term	Safety Set
14.3.4.1.1	Summary of Clinical Chemistry	Safety Set
14.3.4.1.2	Shift of Clinical Chemistry	Safety Set
14.3.4.1.3	Potentially Clinically Significant (PCS) Values in Clinical Chemistry Excluding Liver Function Tests	Safety Set
14.3.4.1.4	Potentially Clinically Significant (PCS) Values in Liver Function Tests Any Time Post-baseline	Safety Set
14.3.4.2.1	Summary of Hematology	Safety Set
14.3.4.2.2	Shift of Hematology	Safety Set
14.3.4.2.3	Potentially Clinically Significant (PCS) Values in Hematology	Safety Set
14.3.4.3.1	Summary of Coagulation	Safety Set
14.3.4.3.2	Shift of Coagulation	Safety Set

14.3.4.3.3	Potentially Clinically Significant (PCS) Values in Coagulation	Safety Set
14.3.4.4.1.1	Summary of Urinalysis, Continuous Parameters	Safety Set
14.3.4.4.1.2	Summary of Urinalysis, Categorical Parameters	Safety Set
14.3.4.4.2	Shift of Urinalysis	Safety Set
14.3.4.5.1	Summary of 12-Lead Electrocardiogram	Safety Set
14.3.4.5.2	Shift of Overall Electrocardiogram Interpretation	Safety Set
14.3.4.5.3	Potentially Clinically Significant (PCS) QTcF Values	Safety Set
14.3.4.6.1	Summary of Vital Signs	Safety Set
14.3.4.6.2	Potentially Clinically Significant (PCS) Values in Vital Signs	Safety Set
14.3.4.7.1	Summary of Columbia-Suicide Severity Rating Scale	Safety Set
14.3.4.7.2	Shift From Baseline in Columbia-Suicide Severity Rating Scale (C-SSRS) Suicidal Ideation and Suicidal Behavior by Study Visit	Safety Set
14.3.4.7.3	Shift From Baseline in Columbia-Suicide Severity Rating Scale (C-SSRS) Maximum Severity Score in Suicidal Ideation at Any Time Post-baseline	Safety Set
14.3.4.8	Summary of Physician Withdrawal Checklist (PWC-20)	Safety Set
14.3.4.9.1	Summary of Epworth Sleepiness Scale – Individual Items	Safety Set
14.3.4.9.2	Summary of Epworth Sleepiness Scale – Total Score	Safety Set

Listings		
16.2.1.1	Participant Disposition	All Participants
16.2.1.2	Screen Failures	Screen Failure Participants
16.2.2.1	Inclusion/Exclusion Criteria Violations	All Participants, Excluding Screen Failures
16.2.2.2	Protocol Deviations	Safety Set
16.2.3	Analysis Sets	All Participants
16.2.4.1	Demographics and Informed Consent	Safety Set
16.2.4.2	Child-bearing Potential	Safety Set
16.2.4.3.1	Medical/Surgical History	Safety Set
16.2.4.3.2	Essential Tremor Disease History	Safety Set
16.2.4.4.1	Prior Medications	Safety Set
16.2.4.4.2	Concomitant Medications	Safety Set
16.2.4.5	Concomitant Procedures	Safety Set
16.2.5.1	Investigational Product Dispensation and Return	Safety Set
16.2.5.2.1	Investigational Product Administration – Daily Dosing Diary	Safety Set
16.2.5.2.2	Investigational Product Administration – Log Records	Safety Set
16.2.5.3	Investigational Product Exposure and Adherence	Safety Set
[redacted]		

[redacted]

16.2.7.1	Adverse Events	Safety Set
16.2.7.2	Serious Adverse Events	Safety Set
16.2.7.3	Deaths	Safety Set
16.2.7.4	Adverse Events Leading to Investigational Product Discontinuation	Safety Set
16.2.7.5	Adverse Events Leading to Study Discontinuation	Safety Set
16.2.8.1.1	Clinical Chemistry	Safety Set
16.2.8.1.2	Clinical Hematology	Safety Set
16.2.8.1.3	Clinical Coagulation	Safety Set
16.2.8.1.4	Urinalysis	Safety Set
16.2.8.2.1	Pregnancy Test	Safety Set
16.2.8.2.2	FSH Testing	Safety Set
16.2.8.2.3	Local Drug Screen	Safety Set
16.2.8.2.4	Local Alcohol Screen	Safety Set

16.2.8.2.5	Central Laboratory Drug Screen	Safety Set
16.2.8.3	12-Lead Electrocardiogram (ECG)	Safety Set
16.2.8.4	Vital Signs	Safety Set
16.2.8.5	Physical Examinations	Safety Set
16.2.8.6	Mental Status Examination	Safety Set
16.2.8.7	Abbreviated Neurological Examination	Safety Set
16.2.8.10	Columbia-Suicide Severity Rating Scale (C-SSRS)	Safety Set
16.2.8.11	Physician Withdrawal Checklist	Safety Set
16.2.8.12	Epworth Sleepiness Scale	Safety Set

Certificate Of Completion

Envelope Id: 1171D0B2DF2443FCAB7EBD0FEEFD3DF8
Status: Completed
Subject: Sage_324-ETD-303_sap_v1.0_20241022_methods.pdf
Source Envelope:
Document Pages: 53
Signatures: 7
Envelope Originator:
Certificate Pages: 6
Initials: 0
[redacted]
AutoNav: Enabled
IP Address: [redacted]
EnvelopeId Stamping: Enabled
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Status: Original
23-Oct-2024 | 09:29
Holder: [redacted]
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Signer Events	Signature	Timestamp
[redacted] Sage Therapeutics Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Uploaded Signature Image Signature ID: 28381C0A-811F-448C-A297-569013A4FF00 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23-Oct-2024 | 09:32 Resent: 23-Oct-2024 | 20:53 Viewed: 24-Oct-2024 | 08:44 Signed: 24-Oct-2024 | 08:45
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 95A42B3B-78C2-4820-B3C9-63A26F4312B3 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23-Oct-2024 | 09:32 Viewed: 23-Oct-2024 | 11:22 Signed: 23-Oct-2024 | 11:23
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] Sage Therapeutics - Part 11 Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 104D24A1-5373-4DB6-9066-E2ED46A7602E Using IP Address: [redacted] Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23-Oct-2024 | 09:32 Resent: 23-Oct-2024 | 20:53 Viewed: 23-Oct-2024 | 21:09 Signed: 23-Oct-2024 | 21:11
Electronic Record and Signature Disclosure:		

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[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 4CB4D7BF-3097-4239-AC1B-C40A2362AF78 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 23-Oct-2024 | 09:32 Viewed: 23-Oct-2024 | 09:37 Signed: 23-Oct-2024 | 09:38
Electronic Record and Signature Disclosure: Accepted: 20-Jul-2021 | 11:15 ID: fd75acbc-bffa-47ad-933d-bb55286e892e		
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: B8851932-B1EB-4F32-B640-96A5FE300A64 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23-Oct-2024 | 09:32 Viewed: 23-Oct-2024 | 09:36 Signed: 23-Oct-2024 | 09:37
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[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 67C05255-8C9B-4377-9514-2BB8E4ABBAE9 Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23-Oct-2024 | 09:32 Viewed: 23-Oct-2024 | 09:53 Signed: 23-Oct-2024 | 11:50
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] Security Level: Email, Account Authentication (Required)	[redacted] Signature Adoption: Pre-selected Style Signature ID: 3EEED344-DA9D-425B-9915-C78423F5271E Using IP Address: [redacted] With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 23-Oct-2024 | 09:32 Viewed: 23-Oct-2024 | 09:52 Signed: 23-Oct-2024 | 09:54

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In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	23-Oct-2024 | 09:32
Certified Delivered	Security Checked	23-Oct-2024 | 09:52
Signing Complete	Security Checked	23-Oct-2024 | 09:54
Completed	Security Checked	24-Oct-2024 | 08:45

Payment Events	Status	Timestamps

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