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9. DOCUMENTATION OF STATISTICAL METHODS

The following statistical analysis plan is provided:

SAGE-324-ETD-202 SAP v1.0 – 17 June 2024

STATISTICAL ANALYSIS PLAN
METHODS
PROTOCOL NUMBER 324-ETD-202

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

Author(s) of SAP: [redacted]

Version: 1.0

Version Date of SAP: 17-June-2024

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

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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
ADL	activities of daily living
AR(1)	Autoregressive (1)
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End-of-Study
EOT	End of Treatment
[redacted]	[redacted]
[redacted]	[redacted]
ET	essential tremor
ETV	Early Termination Visit
IP	investigational product
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Effects Model for Repeated Measures
[redacted]	[redacted]
PCS	potentially clinically significant
PCSC	potentially clinically significant change
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PT	Preferred Term
[redacted]	[redacted]

Abbreviation	Definition
QTcF	QT corrected according to Fridericia's formula
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
WHO-DD	World Health Organization Drug Dictionary

2. INTRODUCTION

This SAP is for the final analysis of clinical study protocol SAGE-324-ETD-202 and is based on the approved clinical study protocol, dated on 02 November 2023, Version 6.0.

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 evaluate the dose-response relationship of different doses of SAGE-324 on upper extremity tremor in the monotherapy cohort.

3.2. Secondary Objectives

The secondary objective of this study is to evaluate the dose-response relationship of different doses of SAGE-324 on specified activities of daily living (ADL) in the monotherapy cohort.

4. STUDY ENDPOINTS

4.1. Efficacy Endpoint

4.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is the change from baseline in TETRAS Performance Subscale Item 4 (upper limb) total score on Day 91 in the monotherapy cohort.

4.1.2. Secondary Efficacy Endpoint

The secondary efficacy endpoint of this study is the change from baseline in TETRAS ADL composite score in the monotherapy cohort.

4.1.3. Primary and Secondary Efficacy Endpoint Estimand

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

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

[redacted]

[redacted]

4.2. Safety Endpoints

The safety endpoints of this study are:

- Incidence of treatment-emergent adverse events (TEAEs)
- Change from baseline in vital signs
- Change from baseline in electrocardiogram (ECG) parameters
- Change from baseline in clinical laboratory parameters (eg, serum chemistry, hematology, coagulation, and urinalysis)

[redacted]

5. STUDY DESIGN

5.1. Overall Design

This study is a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy, safety, and tolerability of SAGE-324 in participants with ET. Participants, site staff, and sponsor personnel will be blinded to treatment allocations. This study includes a Screening Period of up to 28 days, a 90-day double-blind Treatment Period (90 days of dosing), and a 14-day Follow-up Period. See the Schedule of Assessments (Appendix A) for the full list of study assessments and timings. A schematic of the study is presented in Figure 1.

Participants who have provided informed consent will undergo screening assessments to determine eligibility. The Screening Period may be extended for an additional 14 days (to a total of 42 days) for subjects requiring additional time to taper ET medication (other than propranolol), after approval from the sponsor.

Following completion of screening and Day 1 eligibility assessments, participants will be randomly assigned to 1 of 4 treatment groups (placebo or SAGE-324: 15 mg, 30 mg, or 60 mg, oral daily) in a 1:1:1:1 ratio, stratified by baseline propranolol use (adjunct therapy).

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

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

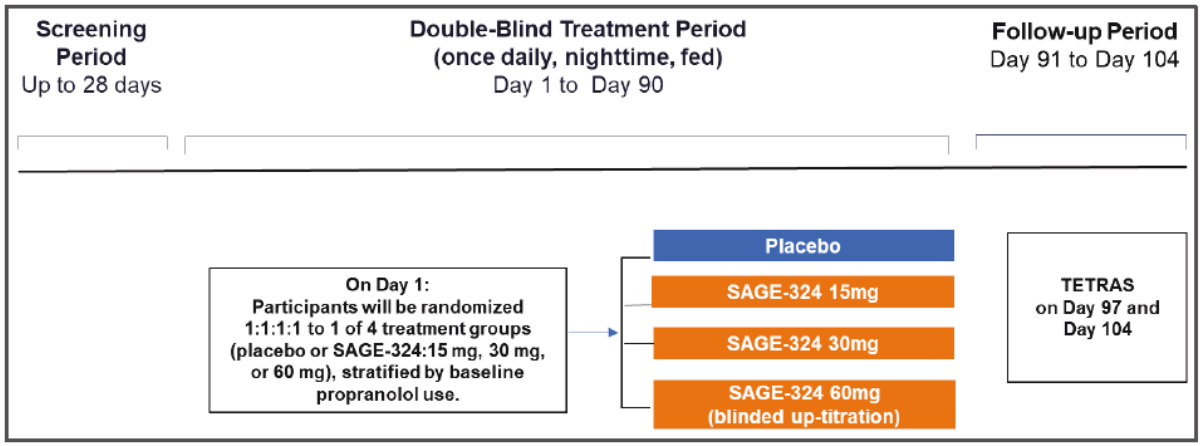
The 60-mg dose group will receive 15 mg of SAGE-324 from Day 1 to Day 14, then 30 mg from Day 15 to Day 28, then 45 mg from Day 29 to Day 42, and then 60 mg from Day 43 to Day 90.

Starting on Day 1, after randomization, participants will receive a single dose of IP once daily for 90 days on an outpatient basis, to be taken before bed, with a snack if bedtime is not within 2 hours of the evening meal. During the Treatment Period, participants will return to the study center for efficacy and safety assessments as specified in Appendix A.

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

No dose reductions of SAGE-324 will be permitted.

Figure 1: Study Design



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

5.2. Sample Size and Power

The planned sample size is 160 participants, randomized in a 1:1:1:1 ratio to each of the dose groups (placebo and SAGE-324: 15 mg, 30 mg, and 60 mg), stratified by baseline propranolol use, with at least 104 (65%, 26 participants per dose group) monotherapy participants and up to 56 (35%, 14 participants per dose group) adjunct therapy participants.

The sample size of 104 participants for the monotherapy cohort assumes a change from baseline at Day 91 in TETRAS upper limb Item 4 score for the placebo group of -1.2 points, a maximum decrease of -3.2 points from Baseline for a dose response in the 15-60mg dose groups with a standard deviation of 2.5.

Under these assumptions with a few prespecified candidate dose-response models, including linear, loglinear, quadratic, exponential, logistic, Emax, sigEmax, and beta as shown in Figure 2 (see Section 8.3.3.1 of this analysis plan for underlying parameters associated with each model), a sample size of 22 evaluable participants per group would provide 80% power for demonstrating a nonflat dose-response relationship by Multiple Comparisons Procedure - Modeling (MCP-Mod) approach, using a 1-sided type I error rate of 0.05.

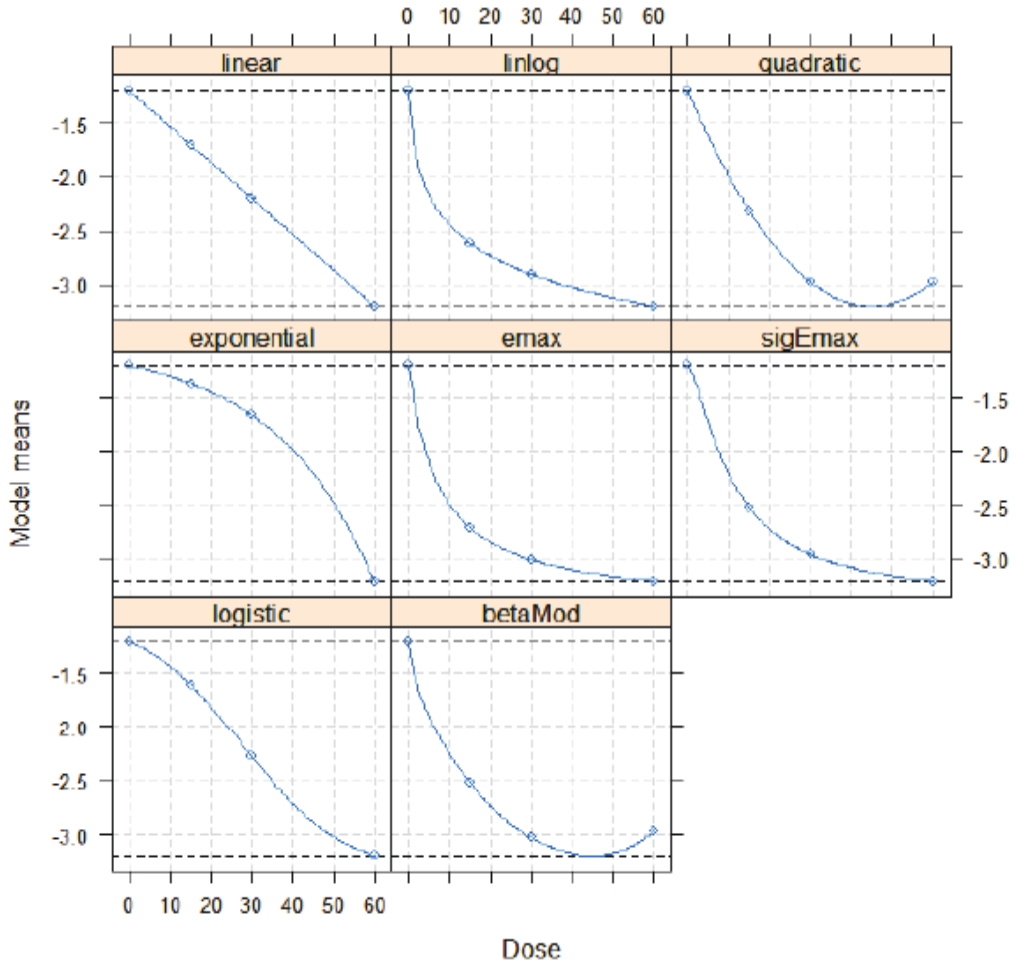
Assuming a nonevaluable rate of 15% across all treatment groups, approximately 104 participants (26 per treatment group) will be randomized. Additional participants may be enrolled if the overall nonevaluable rate is higher than 20%.

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

A blinded interim look of the primary and secondary endpoint data may be conducted to evaluate the sample size assumptions. Additional participants may be randomized if the

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

Figure 2: Prespecified Dose Response Models



5.3. Randomization

This is a randomized, double-blind, placebo-controlled study. Participants will be randomized in a 1:1:1:1 ratio to treatment groups (15 mg, 30 mg, 60 mg SAGE-324, or placebo), stratified by baseline propranolol use. Randomization schedules will be generated by an independent statistician, and randomization to treatment group according to the randomization schedule will be performed centrally via an interactive response technology system.

5.4. Blinding and Unblinding

This is a randomized, double-blind, placebo-controlled study. Participants, site staff, and the study team will be blinded to treatment allocation during the study. The randomization

schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

During the study, the blind is to be broken only when the safety of a participant is at risk and the treatment plan is dependent on the study treatment received. Unless a participant is at immediate risk, the investigator should make diligent attempts to contact Sage prior to unblinding the study treatment administered to a participant. If the unblinding occurs without Sage's knowledge, the investigator must notify Sage within 24 hours of breaking the blind.

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

6. MODIFICATIONS

6.1. Modifications from the Approved Clinical Study Protocol

Protocol Amendment 3 (Version 4.0 dated 07-Oct-2022) permitted alcohol consumption with restrictions on amount and timing with respect to scheduled study visits. The summarization and main analysis of the primary endpoint will be repeated for categories of whether alcohol historically helped tremor (see Section 8.3.3.4).

Protocol Amendment 4 (Version 5.0 dated 10-Jan-2023) included an update to eligibility criteria and statistical analyses to include participants who are receiving propranolol for the treatment of essential tremor.

- Objectives and endpoints were updated to include the monotherapy cohort (SAGE-324), adjunct therapy cohort (SAGE-324 + propranolol), and overall population.
- Sample size and power were updated to focus on required enrollment for monotherapy participants; the adjunct therapy cohort was not based on statistical significance, but clinical considerations.
- Randomization was stratified by baseline propranolol use.
- Summarization and analysis of the primary efficacy variable, secondary efficacy variables [redacted] was updated to be performed for the monotherapy cohort (primary cohort), adjunct therapy cohort (for directional investigation, excluding MCP-Mod analysis), and overall.
- [redacted]

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. Also note that no interim analysis was performed in this study.

7. ANALYSIS SETS

7.1. All Participants Set

The All Participants Set will include all participants who have given written informed consent and participated in the screening process. This analysis set will be used for all listings and disposition.

7.2. Efficacy Analysis Sets

7.2.1. Full Analysis Set

The Full Analysis Set will include all randomized participants who received any amount of IP and have a baseline and at least one post-baseline TETRAS Performance Subscale Item 4 (upper limb tremor) total score.

7.2.2. Per Protocol Set

The Per Protocol Set will include all participants in the Full Analysis Set without any major protocol deviations that could affect efficacy. The review of major protocol deviations will be completed and the decision on whether the deviation affects efficacy and results in removal of a participant from the Per Protocol Set will be documented before database unblinding. The Per Protocol Set will exclude full analysis set participants satisfying any of the following conditions:

- Study Drug Adherence (defined in Section 8.2.7) < 75%
- Inappropriate drug consumption (typically due to incorrect kit dispensation): if the participant consumed at any time during the study any study drug that the participant is not randomized to
- Day 91 efficacy assessment done 3 days or more after the last dose
- Essential tremor duration of less than 3 years
- Prohibited essential tremor medication during the treatment phase of the study (after completing the treatment is fine)
- Any other major protocol deviations that the protocol deviation review committee (PDRC) documents as impacting the primary efficacy analysis prior to the database lock.

7.3. Safety Analysis Set

The Safety Analysis Set is defined as all participants administered IP. The Safety Analysis Set will be used for safety analysis.

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. All summaries will be provided by treatment group.

For all safety and efficacy analyses where applicable, baseline is defined as the last non-missing measurement prior to the first dose of IP. A baseline composite endpoint will be calculated based on baseline individual endpoints.

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. In general, 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; source data reported to several decimal places will be reported to an appropriate number of decimals places as determined by the study team. 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 variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place unless otherwise specified.

Participants will be summarized according to randomized treatment for all analyses except for safety analyses. For safety analyses, participants will be summarized according to treatment received.

P-values will be reported to four decimal places, with p-values less than 0.0001 reported as "<0.0001". P-values larger than 0.9999 will be reported as ">0.9999".

8.2. Background Characteristics

8.2.1. Participant Disposition

The summaries of disposition will include number of participants who were screened (All Participants Set), who were randomized, who received study drug, the number and percentage of participants who completed the study and who prematurely withdrew from the study, primary reasons for not completing the study, who completed treatment, who discontinued treatment prematurely, and primary reasons for discontinuing treatment.

Study completion summary and treatment completion summary will be based on participants who received study drug (Safety Analysis Set). Percentages will be calculated based on the participants randomized and dosed. These data will be provided by randomized treatment groups, by stratum (monotherapy cohort and adjunct therapy cohort) and overall.

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, this participant will be counted only once.

The number of participants in each of the analysis sets will also be summarized and presented by treatment arm, by stratum (monotherapy cohort and adjunct therapy cohort) and overall. Randomization data (date and time of randomization, randomization number, and randomized treatment) and participants excluded from each analysis set will be listed but not summarized.

A completer for the study is defined as one who completed all study phases, including the final follow-up visit (Day 104 visit) and is derived from the Study Disposition CRF page with completion question answered Yes. A participant is defined as prematurely discontinuing treatment if treatment ends before the final dose of study drug taken on Day 90, and is derived from the Study Treatment Completion/Discontinuation CRF page with completion question answered No. The primary reason for study discontinuation or treatment discontinuation of a participant is provided in the respective CRF page.

8.2.2. Protocol Deviations

Protocol deviations will be captured on the eCRF and categorized by the study team as major and minor deviations without any unblinding information. The major deviations will be summarized by type and by randomized treatment using the Full Analysis Set. The minor deviations will be included in the listing. The COVID-19 related protocol deviations will also be summarized. Summarization will be done by stratum (monotherapy cohort and adjunct therapy cohort) and overall.

Inclusion/exclusion violations will be listed but not summarized.

8.2.3. Demographics and Baseline Characteristics

Demographic data (age, sex, race, and ethnicity) and baseline characteristics (height, weight, BMI, dominant upper limb) will be summarized with descriptive statistics by treatment group using the Safety Analysis Set. This summarization will be done by stratum (monotherapy cohort and adjunct therapy cohort) and overall.

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)

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

8.2.4. Medical/Surgical History

Summarization of medical and surgical history data will be done by stratum (monotherapy cohort and adjunct therapy cohort) and overall.

Medical/surgical history will be coded to Medical Dictionary for Regulatory Activities (MedDRA) terms, using Version 24.1, 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) by treatment group for the Safety Analysis Set.

Medical history related to ET including age at diagnosis, age at onset of ET, tremor responsiveness to alcohol, past treatments for ET, response to therapy, and reason for discontinuation will be listed. Age at diagnosis, age at onset of ET, past treatment for ET (yes/no), and whether alcohol helps participant tremor will also be summarized.

The disease subgroups 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 years, 3 to <6 years, 6 to 10 years, >10 years)
- Years since participant thinks ET started (<3 years, 3 to <6 years, 6 to 10 years, >10 years)
- Alcohol helps tremor: 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), NA
- Reason for discontinuation of past treatment for ET (drug interactions, lack of efficacy, physician decision, side effects, other)

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 September 2021, or later.

All medications taken within 30 days prior to signing the 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); all psychotropic medications taken in the 30 days prior to screening and all medications taken at any time prior to signing the informed consent through the duration of the study for ET will also be recorded.

Those medications taken prior and having use ending 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 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 for the Safety Analysis Set as the number and percentage of participants with each medication at both the ATC and PT levels; these summarizations will be done by stratum (monotherapy cohort and adjunct therapy cohort) and overall. Details of prior and concomitant medications will be listed by participant, start date, and verbatim term.

8.2.6. Investigational Product Exposure

Total drug exposure (in mg) is defined as the total IP in mg for SAGE-324 that was taken during the study. Total drug exposure for participants randomized to placebo is zero unless the participant has taken SAGE-324 by mistake, in which case the total drug exposure comes from SAGE-324 exposure. If a participant skips a dose on any of the days, the dose taken is 0 mg.

Total exposure duration to IP (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.

For participants that have been dispensed with SAGE-324 15mg, 30mg, and 45mg pre-packed kit, but do not take the full 4 tablets, from a safety perspective, the general rule is that the tablets taken are assumed to be the active tablet(s) in the dispensed kit before counting any placebo tablets. For example, for a 15mg pre-packed kit, if the patient takes only one tablet, the tablet would be the 15mg tablet. If the patient takes 2 tablets, it would be assumed that they took the one 15mg tablet and one placebo tablet.

Planned exposure for the participants who complete the treatment period is defined as follows:

1. For participants randomized to the SAGE-324 15 mg group, 90 days of treatment times 15 mg
2. For participants randomized to the SAGE-324 30 mg group, 90 days of treatment times 30 mg
3. For participants randomized to the SAGE-324 60 mg group, the sum of 14 days of treatment times 15 mg, 14 days of treatment times 30 mg, 14 days of treatment times 45 mg, and 48 days of treatment times 60 mg

Planned exposure for the participants who discontinue the treatment period early is defined as follows:

1. For participants randomized to the SAGE-324 15 mg group, total exposure duration times 15 mg

2. For participants randomized to the SAGE-324 30 mg group, total exposure duration times 30 mg
3. For participants randomized to the SAGE-324 60 mg treatment group
    - If 1 ≤ total exposure duration ≤ 14, then planned exposure = total exposure duration times 15 mg
    - If 15 ≤ total exposure duration ≤ 28, then planned exposure = 14 days times 15 mg + (total exposure duration - 14) times 30 mg
    - If 29≤ total exposure duration ≤ 42, then planned exposure = 14 days times 15 mg + 14 days times 30 mg + (total exposure duration - 28) times 45 mg
    - If 43 ≤ total exposure duration ≤ 90, then planned exposure = 14 days times 15 mg + 14 days times 30 mg + 14 days times 45 mg + (total exposure duration - 42) times 60 mg

For participants randomized to placebo, planned exposure is not applicable.

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

Total drug exposure, total exposure duration, and percent of planned exposure received will be summarized using the Safety Analysis Set by randomized treatment group. Also, the number and percentage of participants with percent of planned exposure <80%, 80% to <100%, and ≥100% will be summarized. Summarization will be provided by stratum (monotherapy cohort and adjunct therapy cohort) and overall.

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.

The schedule of IP administration is that all participants will take 4 tablets per day in a mix of active and placebo tablets to achieve a dose of 15 mg (1 SAGE-324 tablet and 3 placebo tablets per dose), 30 mg (2 SAGE-324 tablets and 2 placebo tablets per dose) or 60 mg (4 SAGE-324 tablets). The number of tablets planned to be taken is defined as 4 times 90 for the participants who complete the treatment period. For participants who discontinue treatment early, the number of tablets planned to be taken is defined as 4 times total exposure duration (see Section 8.2.6).

IP adherence will be summarized using Safety Analysis Set and randomized treatment group. Number and percentage of participants with IP adherence in categories <75%, 75 to 100%, >100% will be provided. Summarization will be provided by stratum (monotherapy cohort and adjunct therapy cohort) and overall.

8.3. Efficacy Analysis

8.3.1. Definition of Efficacy Variable(s)

8.3.1.1. Primary Efficacy Assessment

For the TETRAS Performance Subscale Item 4 (upper limb), three maneuvers/assessments will be completed for both arms, first for the right arm and then for the left, specifically Item 4a, limbs extended forward maneuver (postural tremor), Item 4b, wing-beating [elbows flexed] maneuver (postural tremor), and Item 4c finger-nose-finger maneuver (kinetic tremor). Each assessment is rated on a 0 to 4 scale of severity in 0.5-point increments, with higher scores indicating more severe tremor. The Performance Subscale Item 4 (upper limb) total score range for a given side (left or right) is 0 to 12, and for both sides combined is 0 to 24; if any component of a total score for a side or both sides is missing, the total score is not computed. Assessment of the TETRAS Performance Subscale Item 4 (upper limb) occurs at Screening and Days 1, 8, 15, 29, 43, 57, 71, 91/EOT, and 97.

The primary efficacy endpoint is the change from baseline in TETRAS Performance Subscale Item 4 (upper limb) total score at Day 91 in the monotherapy cohort for the Full Analysis Set.

8.3.1.2. Secondary Efficacy Assessment

The TETRAS ADL Subscale assesses how ET affects typical activities of daily living (ie, speech, eating, drinking, dressing, personal hygiene, writing, occupational impairment, social impact, and activities affected by upper limb tremor). It consists of 12 items that are each rated on a scale from 0 (normal activity) to 4 (severe abnormality), and the overall ADL score range is 0 to 48; if any component of overall ADL score is missing, the overall ADL score is not computed. Responses of 0 and 1 in TETRAS ADL Subscale Items 1 to 11 will be collapsed and analyzed as a single response of 0 = normal/slightly abnormal such that the scale becomes:

0 = Normal/slightly abnormal

1 = Mildly abnormal

2 = Moderately abnormal

3 = Severely abnormal

TETRAS Performance Subscale Item 6 (Archimedes Spiral) is assessed for both the right and left sides. Each assessment is rated on a 0 to 4 scale of severity, with higher scores indicating more severe tremor. Since Item 6 may be assessed on a scale with 0.5 point increments, the responses of Item 6 will be rescaled as:

0 = Normal/slightly abnormal (original score of 0, 0.5, 1)

1 = Mildly abnormal (original score of 1.5, 2)

2 = Moderately abnormal (original score of 2.5, 3)

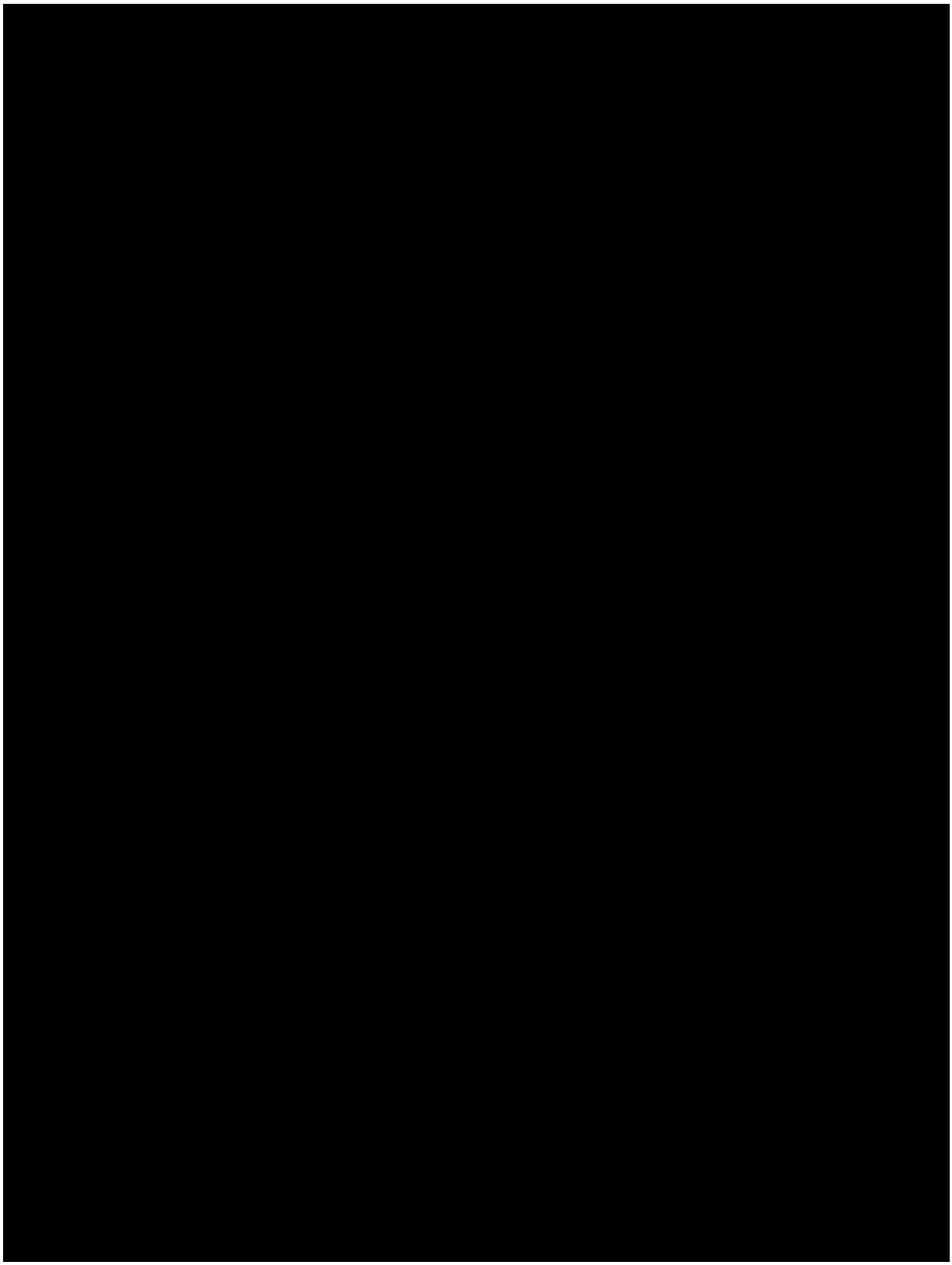
3 = Severely abnormal (original score of 3.5, 4)

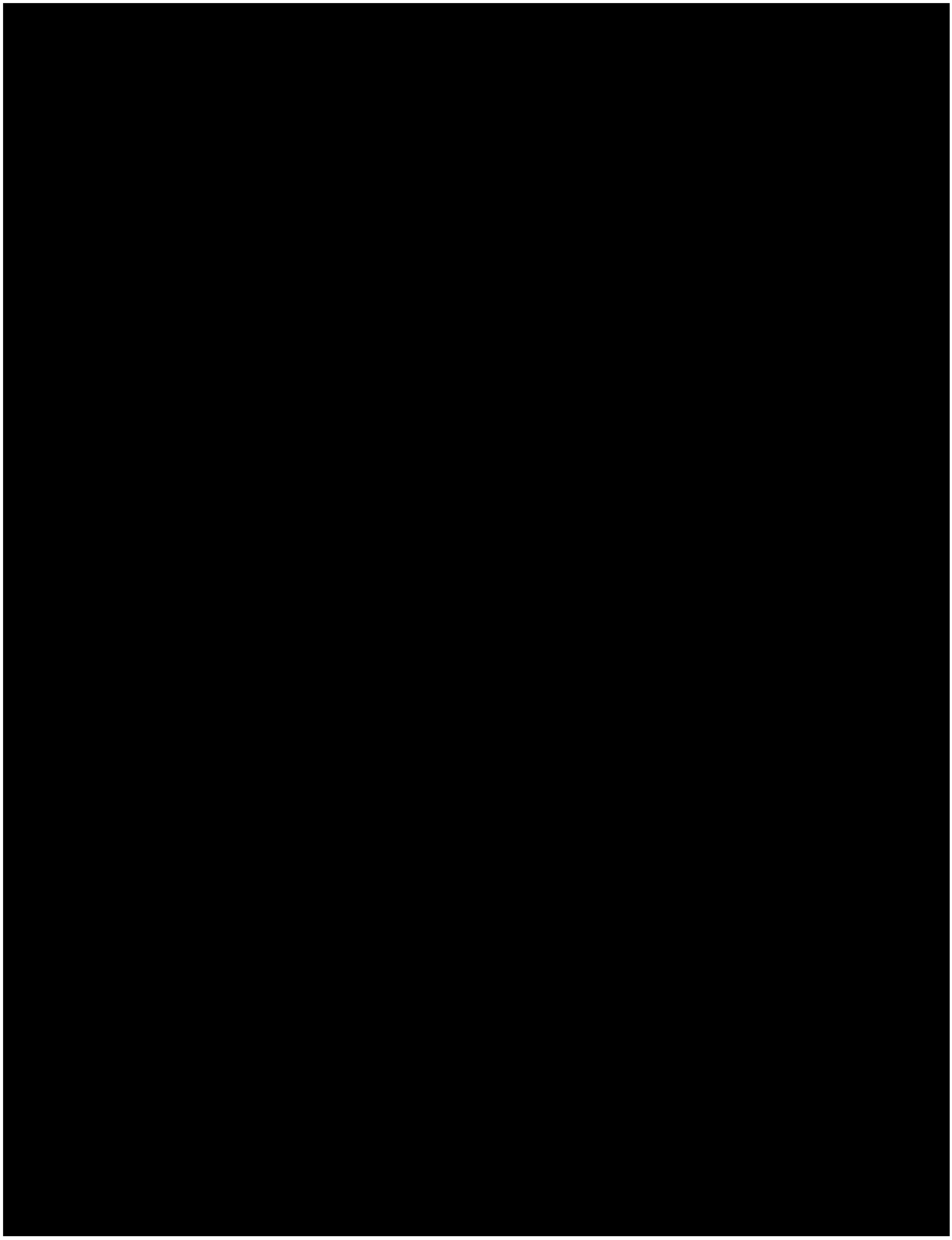
Assessment of the TETRAS ADL and Performance Subscales occurs at Screening and Days 1, 8, 15, 29, 43, 57, 71, 91, and 97.

The TETRAS ADL composite endpoint comprises Items 1 to 11 of the TETRAS ADL Subscale and Item 6 (both sides) of the TETRAS Performance Subscale, and can range in value from 0 to 39; if any component of the TETRAS ADL composite endpoint is missing, the TETRAS ADL composite endpoint is not computed.

The secondary efficacy endpoint is the change from baseline in the TETRAS ADL composite score at Day 91 in the monotherapy cohort for the Full Analysis Set.

[redacted]





[redacted]

[redacted]

8.3.2. Visit Windows for Efficacy Analyses

The scheduled visits will not be windowed and will be used at nominal visit value for treatment and follow-up period visits (Day 1, Day 8, Day 15, Day 29, Day 43, Day 57, Day 71, Day 91, Day 97, Day 104). Unscheduled, end-of-treatment (EOT), and early termination visits (ETV) that happen on or before one day after the last dose will be mapped to a scheduled visit for analysis using the date of collection/assessment and Day 1, first dose date, as a basis to determine study day and then study day will be mapped to the intended visit according to the visit windows specified in the Table 2. Unscheduled, EOT, or ET visits that happen on or after 1 day after the last dose will be windowed using relative days since last dose date; the mapping will follow the visit window in Table 2. To accommodate as much data as possible into analysis, these windows have been widened relative to protocol-specified operational windows to have no gap between them; these windows are used for analysis purposes only.

Table 2: Visit Windows for Efficacy Analysis

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Screening	Day -1	Days -28 to Day -1
Day 1 Predose	Day 1 Predose	Day 1 Predose
Day 8 (±1 day)	8	Day 1 Postdose to Day 11
Day 15 (±1 day)	15	Days 12 to 22
Day 29 (±1 day)	29	Days 23 to 36

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Day 43 (±1 day)	43	Days 37 to 50
Day 57 (±3 days)	57	Days 51 to 64
Day 71 (±3 days)	71	Days 65 to 81
Day 91 (+1 day)	91	Days 82 to 96
Day 97/last dose +7 days (±3 days)	97/last dose+ 7 days	Days 97 to 100 (last dose+6 days, last dose + 10 days)
Day 104/last dose + 14 days (±3 days)(*)	104/last dose + 14 days	≥ Day 101 (last dose + 11 days, last dose + 17 days)

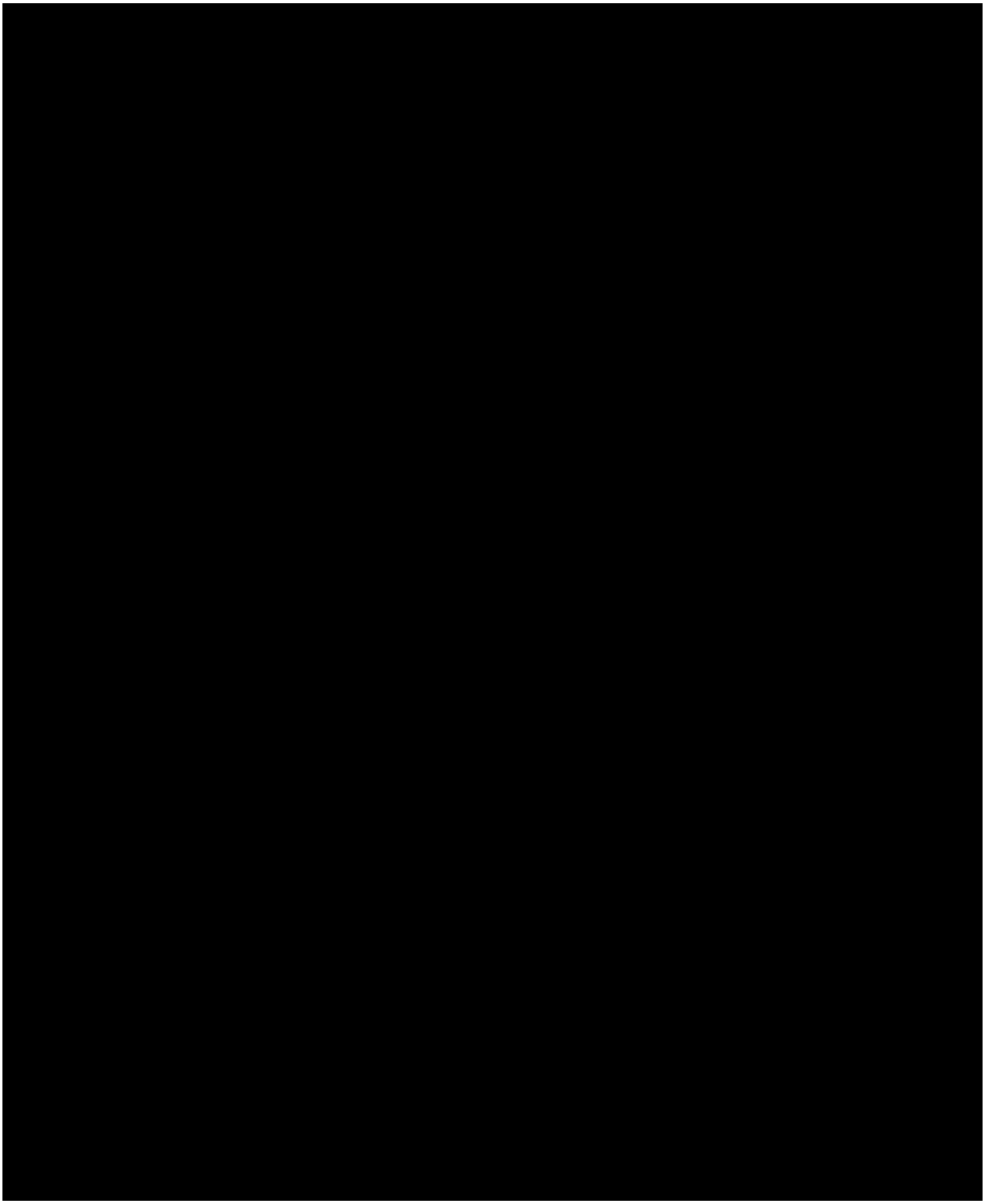
Note: Parenthesized study days and study day windows are for unscheduled, EOT, and ET visits. For participants who have discontinued treatment prematurely with either unscheduled, EOT, or ET visits on or after 6 days of the last dose, those visits should be mapped to Day 97 or Day 104 using the parenthesized visit windows listed (ie, visit date – last dose date >1).
Note: (*) The scheduled visit of Day 104/last dose visit is for efficacy analysis excluding TETRAS.

Once analysis visits are assigned based on the visit windows, all visits, including scheduled visits, unscheduled visits, and EOT/ETV visits, will be eligible for being flagged as the "analyzed record" within the analysis visit window; a participant's individual analysis visit window could potentially contain more than 1 visit. In the event of multiple visits falling within an analysis window or in case of a tie relative to number of days from the scheduled study day, the following rules will be used in sequence to determine the "analyzed record" for the analysis visit window:

- If data from the scheduled visit is available within treatment period, then the scheduled visit data will be used.
- If no data from the scheduled visit within treatment period is available, then the windowed visit data will be used.
- If more than one visit is in the same target day window, the data closest to the target day will be used.
    - If there is a tie with distance from visits to target day, the visit after the the target day will be used.

The summary by visit will use the "analyzed records" only – at most one per participant per visit. The data not flagged as the "analyzed record" will be included in listings. An unscheduled visit that does not fall under any analysis window (e.g. in case one is available after Day 107) will remain in the database and will be included in the listings.

[redacted]



8.3.3. Analysis of Primary Efficacy Variable(s)

The efficacy analysis uses the Full Analysis Set and presents data by randomized treatment, unless specified otherwise. Summarization and analysis of the primary efficacy variable will

be performed for the monotherapy cohort (primary cohort), adjunct therapy cohort (for directional investigation, excluding MCP-Mod analysis), and overall.

8.3.3.1. Primary Analysis

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

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

The observed value, change from baseline, and percent change from baseline of the TETRAS Performance Subscale Item 4 (upper limb tremor) scores (individual and total score by side and combined) will be summarized descriptively by randomized treatment at each scheduled time point.

The primary endpoint will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline TETRAS Performance Subscale Item 4 (upper limb tremor) total score, assessment timepoint, and timepoint-by-treatment as explanatory variables. All explanatory variables will be treated as fixed effects. All postbaseline clinic visits will be included in the model. An unstructured covariance structure will be used to model the within-participant errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If there is a convergence issue with the unstructured covariance model, Toeplitz or Autoregressive (1) [AR(1)] covariance structure will be used, following this sequence until convergence is achieved. When the covariance structure is not unstructured, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS. A pairwise comparison of change from baseline in TETRAS Performance Subscale Item 4

(upper limb tremor) for each SAGE-324 treatment group versus placebo will be provided. The p-values are not adjusted for multiplicity, so should be interpreted as nominal.

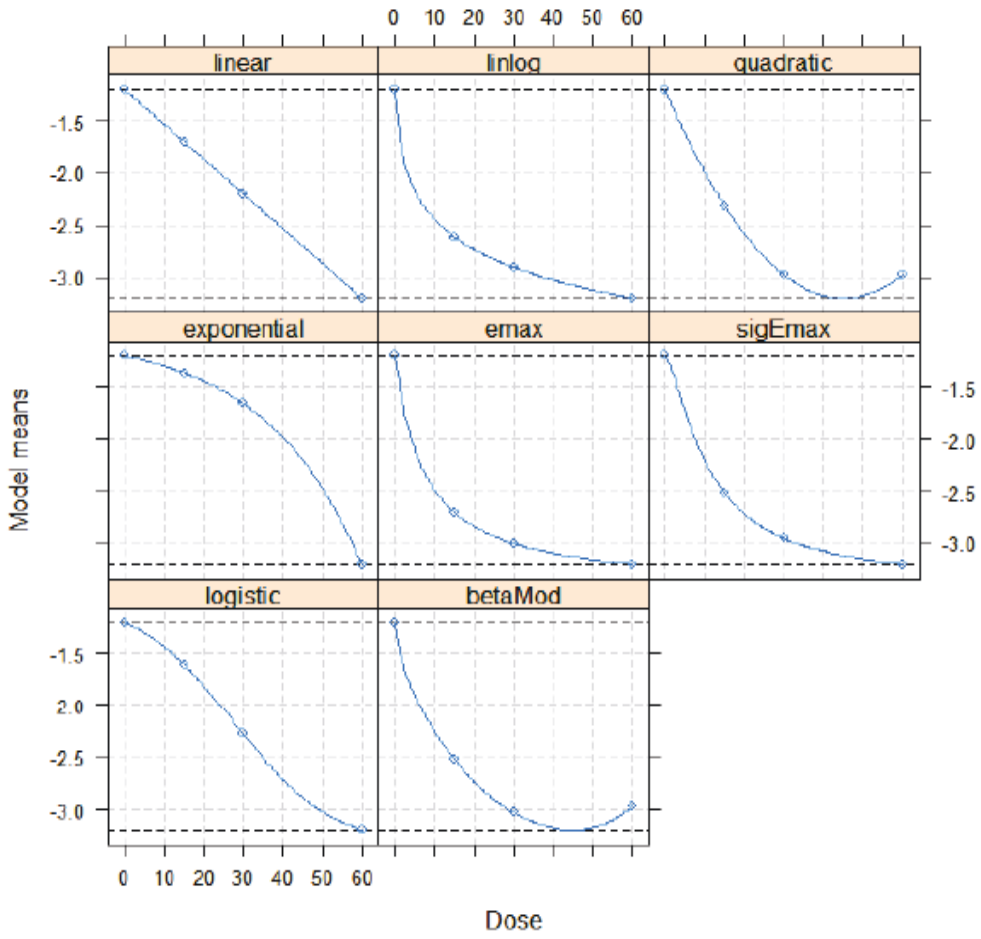
After the MMRM analysis by PROC MIXED, the estimated mean and covariance matrix at Day 91 will be passed to the MCP-Mod analysis (Bretz F, Pinheiro JC, Branson M, 2005) to test the dose-response relationship. A critical value will be determined from the joint multivariate normal distribution of the contrast test statistics at the overall one-sided alpha level of 0.05. If the test statistic exceeds this critical value, a nonflat dose-response relationship will be demonstrated.

In the analysis, multiple dose-response candidate models will be considered, including linear, loglinear, quadratic, exponential, logistic, Emax, sigEmax, and beta. In the trial design stage, these pre-specified candidate models based on available information were included in the MCP-Mod procedure. The parameters used to determine the contrast for testing assumes a change from baseline in TETRAS Item 4 upper limb total score in the placebo group of -1.2 points, a maximum decrease of -3.2 points from baseline for a dose response in the 15 to 60-mg dose groups. These can be done using the DoseFinding Package in R.

```
doses <- c(0, 15, 30, 60)

pboeff  <- -1.2
acteff  <- -2
quad    <- guesst (d=45, p=1, 'quadratic')
exp     <- guesst (d=45, p=0.5, 'exponential', Maxd=60)
emax    <- guesst(d=30, p=0.8, 'emax')
sigemax <- guesst (d=c(15, 30), p=c (0.6, 0.8), 'sigEmax')
logis   <- guesst (d=c(10, 45), p=c( 0.2, 0.8), model='logistic')
beta<- guesst(d=30, p=0.8, model='betaMod', dMax=45, scal=65, Maxd=60)

my.model <-Mods(linear=NULL,
                linlog=NULL,
                quadratic=quad,
                exponential=exp,
                emax=emax,
                sigEmax=sigemax,
                logistic=logis,
                betaMod=beta,
                doses=doses,
                placEff=pboeff,
                maxEff=acteff)
plot(my.model)
```



The optimal contrast coefficients are used to identify the best matching model, which can be computed with "optContr" function. It requires input of matrix. In this example it uses the covariance matrix exported from SAS, using repeated measurement analysis (MMRM) by PROC MIXED.

```
ContMatnew <- optContr(my.model, S=cov)
```

Model-specific contrast tests with null hypotheses of a flat dose-response curve are performed by "MCTtest" function. Any model that has t-statistics > critical value is statistically significant.

```
my.test <- MCTtest (dose=dose, resp=estimate, data=xxx, my.mode, S=cov,
                    type='general',
                    placAdj=FALSE, df=Inf,
                    critV=TRUE, pVal=TRUE, alpha=0.05,
                    alternative =c ('one.sided'), na.action=na.fail,
                    mvtcontrol=mvtnorm.control(), contMat=contMatnew)
```

After the MCT test, if any model is significantly different from a flat dose-response curve, the best fit model could be selected.

```
fit.xxx<-fitMod (dose=dose, resp=estimate, data=xxx, my.mode, S=cov,
                    model=xxx, type='general')
```

```
plot(fit.xxx, CI=TRUE, plotData='meanCI', level=0.95)
```

The main comparison will be between SAGE-324 and placebo at Day 91, if a non-flat dose-response relationship is established. Model-based point estimates (ie, least squares mean, 95% confidence intervals, and p-values) will be reported where applicable. Line plots of model-based LS Means and standard errors (SE) over time will be prepared for the primary endpoint.

8.3.3.2. Sensitivity Analysis of Primary Endpoint

Sensitivity analysis of the primary endpoint will be performed to assess the robustness of the primary analysis results in the presence of missing data. For participants who terminate from treatment prior to the end of the analysis period due to adverse event, noncompliance with study procedures, death, physician decision, or use of a prohibited medication, missing measurements will be considered missing not at random (MNAR); for all other participants having missing measurements, missing values will be considered missing completely at random (MCAR).

For FAS monotherapy subjects having missing TETRAS Performance Subscale Item 4 (upper limb tremor) total score data at any visit, and, separately, for FAS subjects overall, all missing data (MCAR or MNAR) will be imputed via multiple imputation (50-100 iterations, depending on system run time) using treatment based regression methodology which includes baseline TETRAS Performance Subscale Item 4 (upper limb tremor) total score in the model, with minimum and maximum possible integer values of 0 to 24, respectively (example SAS code is found in Appendix C). The MMRM model, including the selected covariance structure, used for the main analysis of the primary efficacy endpoint will be repeated for each imputation, and the results combined and reported. The covariance matrices resulting from the MMRM run on each imputation will be combined into an overall covariance matrix via either the COVB or TCOV options of Proc MIANALYZE in SAS; the resulting overall covariance matrix will be passed to the MCP-Mod analysis to perform sensitivity analysis of the dose-response relationship. SAS code associated with this sensitivity analysis is noted in Appendix C.

If the sensitivity analysis yields a result/conclusion that is different from the result of the primary analysis, the nature of the discrepancy will be examined in order to clearly explain the discrepancy based on statistical principles, and the discrepancy will be discussed in the clinical study report.

8.3.3.3. Supportive Analysis of Primary Endpoint

Summarization and analysis of the primary endpoint will be repeated based on the Per Protocol Set as a supportive analysis.

8.3.3.4. Subgroup Analyses of Primary Endpoint

The descriptive summarization and MMRM analysis of the primary endpoint will also be presented by the following subgroups:

- Age group: <65 years, 65 to 80 years

- Sex: Male, Female
- Race: White, Black or African American, Asian, Other
- BMI: <18.5 kg/m^2, 18.5 to <25 kg/m^2, 25 to < 30 kg/m^2, ≥30 kg/m^2
- Age at ET diagnoses: <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: <6 years, 6 to 10 years, and >10 years
- Years since participant thinks ET started: <6 years, 6 to 10 years, and >10 years
- Alcohol helps tremor: Yes (Intermediate, Worked Well), No (No, a little), NA
- Baseline TETRAS performance subscale part 4 upper limb tremor score on the dominant side: <7.5 and ≥7.5
- Baseline TETRAS performance subscale part 4 upper limb tremor score on the dominant side: < median and ≥ median
- Past treatment for ET (Yes, No)
- Response to past treatment for ET: Yes (Intermediate, Worked Well), No (No, a little), NA

If any of the subcategories has <5 patients fall into that category, the category will be combined with the next adjacent category with smaller counts. For example, if the number of patients falling into BMI category <18.5 kg/m^2 is <5, this category will be combined with the 18.5 to <25 kg/m^2 group. In the case of a variable of interest having only 2 subcategories and one of those subcategories has <5 patients, the variable will not be part of the sub-group analysis.

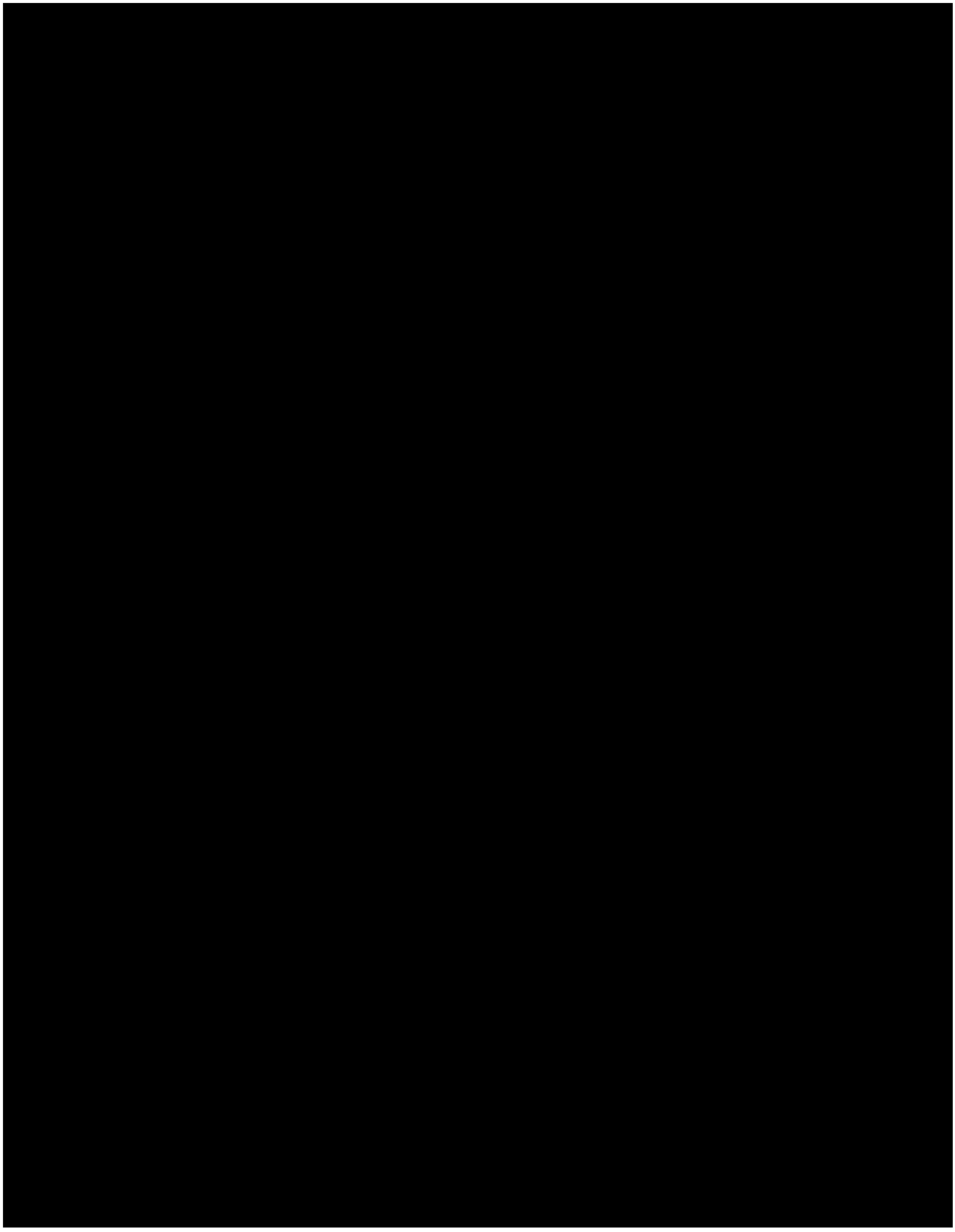
Forest plots for subgroup analysis for the primary endpoint at Day 91 – LS mean differences and associated confidence intervals – will be provided.

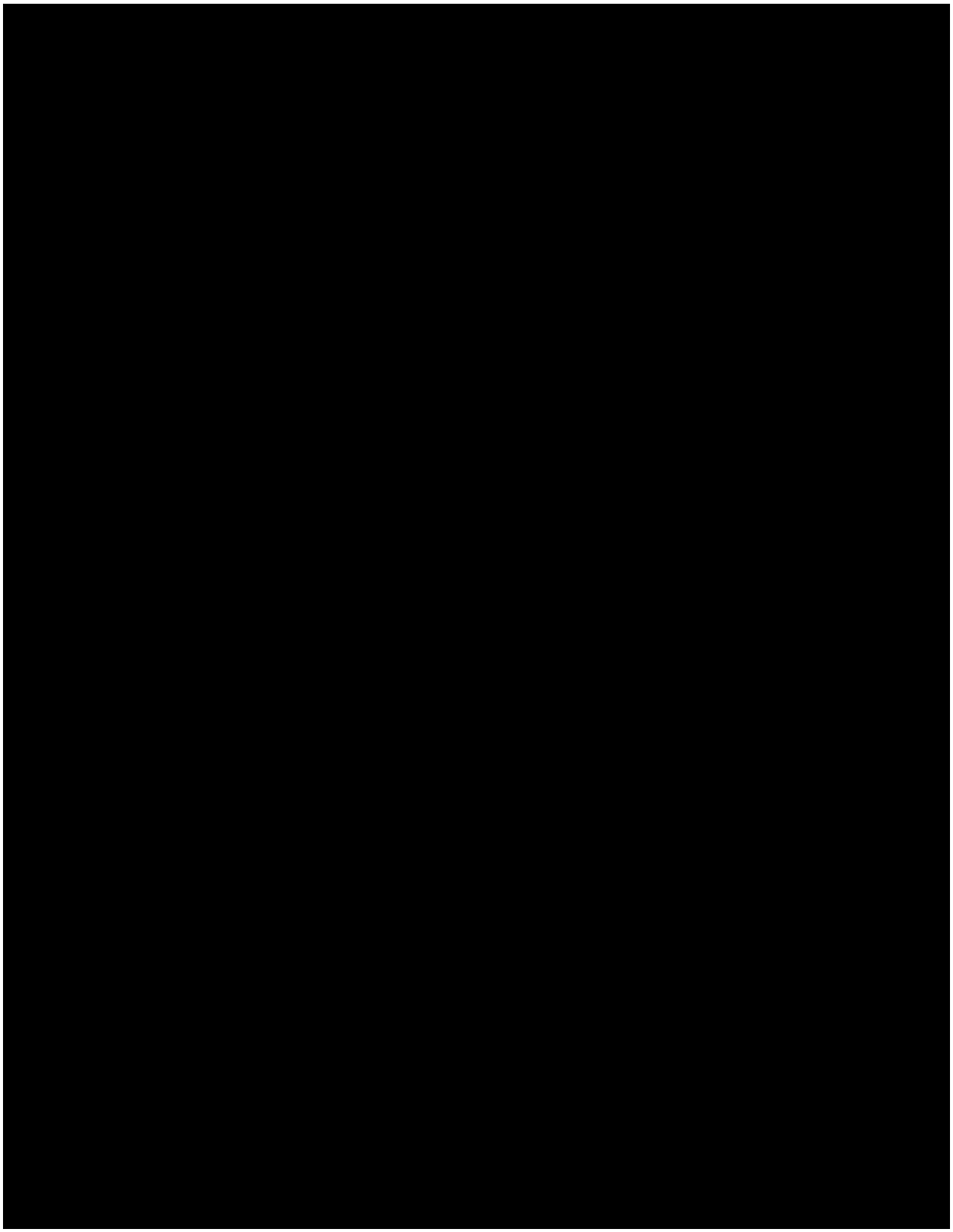
8.3.4. Analysis of Secondary Efficacy Variables

Summarization and analysis of the secondary efficacy variables will be performed for the monotherapy cohort (main analysis), adjunct therapy cohort (for directional investigation, excluding MCP-Mod analysis), and overall.

The primary, sensitivity, supportive, and subgroup analyses performed for the primary endpoint will be repeated for the secondary endpoint, change from baseline in TETRAS ADL composite score.

[redacted]





[redacted]

8.4. Safety Analysis

Safety and tolerability of SAGE-324 will be evaluated by stratum (monotherapy cohort and adjunct therapy cohort) and overall using incidence of TEAEs, vital signs, 12-lead ECGs, clinical laboratory evaluations [redacted]. Safety data will be listed by participant and summarized for each treatment group and SAGE-324 overall.

For safety summary tables, apart from adverse events, the choice of visit records for summarization at a given visit will be following the same rules as described in Section 8.3.2. Additional visit window schedules required for 12-lead ECG and laboratory data (chemistry, hematology, urinalysis, coagulation) appear in Table 6 and Table 7. [redacted]

Table 6: Visit Windows for 12-lead ECG

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Day 1	Day 1	Day ≤1
Day 29 (±1 day)	29	Days 2 to 60
Day 91 (+1 day)	91	Days 61 to 96
Day 104 (±3 days)	104	≥Day 97 (≥ last dose + 6 days)

Note: Parenthesized study days and study day window is for unscheduled, EOT, and ET visits. For participants who have discontinued treatment prematurely with either unscheduled, EOT, or ET visits on or after 6 days of the last dose, those visits should be mapped to Day 104 using the parenthesized visit window listed (ie, visit date – last dose date >1).

Table 7: Visit Windows for Laboratory Data (Chemistry, Hematology, Urinalysis, Coagulation)

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Screening	Day -1	Days -28 to Day -1
Day 1 Predose	Day 1 Predose	Day 1 Predose
Day 8 (±1 day)	8	Day 1 Postdose to Day 11
Day 15 (±1 day)	15	Days 12 to 22
Day 29 (±1 day)	29	Days 23 to 36
Day 43 (±1 day)	43	Days 37 to 50
Day 57 (±3 days)	57	Days 51 to 64
Day 71 (±3 days)	71	Days 64 to 81
Day 91 (+1 day)	91	Days 82 to 96
Day 104 (±3 days)	104	≥ Day 97 (≥ last dose + 6 days)

Note: Parenthesized study days and study day window is for unscheduled, EOT, and ET visits. For participants who have discontinued treatment prematurely with either unscheduled, EOT, or ET visits on or after 6 days of the last dose, those visits should be mapped to Day 104 using the parenthesized visit window listed (ie, visit date – last dose date >1).

All safety summaries will be prepared using the Safety Analysis Set and treatment received. See Table 8 for details on how safety endpoints will be presented. No statistical hypothesis testing will be conducted on the safety data.

Table 8: Presentation of Safety Endpoints

Safety Evaluation	Incidence	Raw Value	Change from Baseline	Clinical Significance	Abnormality	Derived PCS values
AEs	X	*				
Vital Signs		X, *	X			X, *
12-lead ECG		X, *	X	X, *	X, *	X (QTcF only)
Chemistry, Hematology, Urinalysis		X, *	X	X, *	X, *	X
[redacted]						

X = Safety Assessment will be summarized in tables
* = Safety Assessment will be presented in individual participant data listings
Note: Clinical significance and abnormality are based on Investigator review and collected directly from the eCRF.
Note: PCS = Potentially Clinically Significant.

8.4.1. Adverse Events

Adverse events (AEs) will be coded using MedDRA Version 24.1 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 start of IP, or any worsening of a preexisting medical condition/AE with onset at or after the start of IP and throughout the study. A non-TEAE is any adverse event that starts prior to IP. The term IP includes both SAGE-324 and placebo.

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 study treatment discontinuation
- TEAE leading to study discontinuation
- Serious TEAE
- Serious TEAE leading to study treatment 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 discontinuation of treatment or withdrawal from the study and any treatment-emergent SAEs will also be summarized, sorted by descending frequency in SOC and PT within the SAGE-324 group.

The incidence of non-TEAEs will be be summarized by 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 study drug in the following order: related, not related to study drug. An AE with missing severity will be considered as ‘severe’, and with missing relationship to study treatment 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 or worsening 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 treatment 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.

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 summarized as 0.25 mmol/L and potassium recorded as >6.0 mmol/L would be summarized as 6.0 mmol/L.

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

The number and percentage of participants with potentially clinically significant (PCS) values at any time after study drug administration (including unscheduled visits) will be summarized by treatment group for the hematology, chemistry and coagulation parameters defined in Table 9, Table 10, and Table 11, respectively.

Liver function tests will be monitored closely for potentially clinically significant values (Table 12) and will be summarized for occurrence 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 (including coagulation), and urinalysis data will be listed with the values outside the normal ranges flagged. Blood cell morphology and microscopy test results will be listed when available but not summarized. Pregnancy tests, and urine drugs of abuse data will be listed but not summarized.

Table 9: 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 10: 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
HbA1c	%	≥6.5% for nondiabetic patients and >8% for patients with diabetes (at screening) ≥0.25% change from baseline	NA
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
Creatine phosphokinase	U/L	>2xULN	NA
Lactate dehydrogenase	U/L	>2xULN	NA
Liver Function Tests (LFT)			
Bilirubin	µmol/L	>2xULN	NA
Aspartate Aminotransferase	U/L	>3xULN	NA
Alanine Aminotransferase	U/L	>3xULN	NA
Alkaline Phosphatase	U/L	>1.5xULN	NA

Table 11: 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 12: 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)	
Total Bilirubin >2xULN **AND** Alkaline Phosphatase >2xULN **AND** (Alanine Aminotransferase **OR** Aspartate Aminotransferase >3xULN) Total Bilirubin >2xULN **AND** Alkaline Phosphatase <2xULN **AND** [(Alanine Aminotransferase **OR** Aspartate Aminotransferase >3xULN) AND Alkaline Phosphatase <2xULN]	

8.4.3. Electrocardiogram

The average of multiple values collected at one visit will be used for summarization, 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 by treatment group. 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 days (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 visit/timepoint and for any time post-baseline. Potentially clinically significant values will be identified for ECG parameters as outlined in Table 13.

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 and treatment group.

Clinically significant abnormal findings will be reported as adverse events. The average of the multiple values collected at one visit of each parameter will be listed by participant.

Table 13: 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

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 and treatment group. Pulse pressure is defined as [systolic blood pressure - diastolic blood pressure].

The average of multiple values collected at one visit will be used for summarization, including the Day 1 triplicates assessments of supine and standing blood pressure and heart rate.

Potentially clinically significant values will be identified for vital sign parameters as outlined in Table 14. For any post-baseline visit, potentially clinically significant values will be summarized by treatment group and visit.

The number and percentage of participants with orthostatic hypotension, defined as either a decrease in systolic blood pressure of ≥20 mmHg or a decrease in diastolic blood pressure of ≥10 mmHg from supine to standing position, will be summarized by treatment group at each visit. The PCS and orthostatic hypotension at baseline will be evaluated using the average of 3 triplicates.

Vital sign results will be listed by participant and timing of collection.

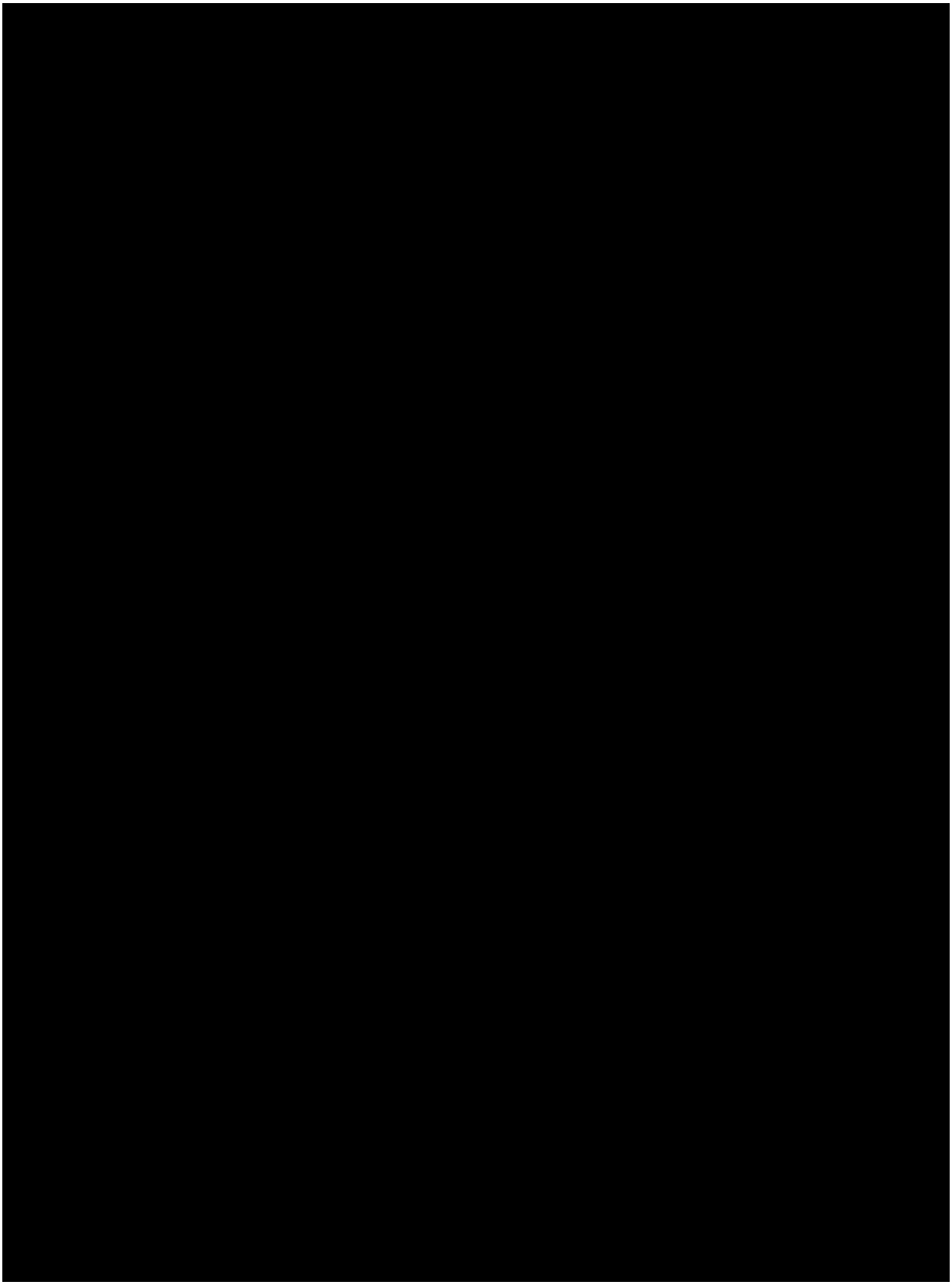
Any vital sign results considered clinically significant by the investigator will be captured as adverse events.

Table 14: 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. After screening, any clinically significant abnormal findings in physical examinations will be reported as AEs.



[redacted]

8.4.9. Other Safety Analysis

Not applicable.

[redacted]

8.7. Other Analysis

Not applicable.

9. SUMMARY OF INTERIM AND DMC ANALYSES

9.1. Interim Analysis

Throughout the enrollment period, a blinded interim look at the primary and secondary endpoint data may be conducted to evaluate the sample size assumptions. If such an interim assessment is scheduled, additional information will be provided in this section. Otherwise, no further details will be included.

9.2. DMC Analysis

Not applicable.

10. REFERENCES

Bretz F, Pinheiro JC, Branson M., Combining multiple comparisons and modeling techniques in dose-response studies., Biometrics. 2005 Sep;61(3):738-48. doi: 10.1111/j.1541-0420.2005.00344.x.

Bjoern Bornkamp, Jose Pinheiro and Frank Bretz (2021). DoseFinding: Planning and Analyzing Dose Finding Experiments. R package version 1.0-2. https://CRAN.R-project.org/package=DoseFinding.

Elble R, Bain P, Forjaz MJ, et al. Task force report: scales for screening and evaluating tremor: critique and recommendations. Mov Disord. 2013 Nov;28(13):1793-800.

11. LIST OF APPENDICES

APPENDIX A. SCHEDULE OF ASSESSMENTS

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

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

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

Abbreviations: AE = adverse event; [redacted] COVID-19 = coronavirus disease 2019; [redacted] ECG = electrocardiogram EOS = end of study; EOT = end of treatment; [redacted] ET = essential tremor; ETV = early termination visit; FSH = follicle stimulating hormone ICF = informed consent form; IP = investigational product; MSE = mental state examination; [redacted] SAE = serious adverse event; TETRAS = The Essential Tremor Rating Assessment Scale; WOCBP = women of childbearing potential.

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

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

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

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

[c] On Day 1, supine and standing blood pressure and heart rate will be collected in triplicate at least 15 minutes apart, measured after the participant has been in the supine position for at least 5 minutes and then repeated 1 minute and 3 minutes after standing. Respiratory rate and temperature are collected once on Day 1.

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

[e] Chemistry, hematology, coagulation, and urinalysis to be collected at all timepoints except Day 97. Note: Myoglobin (urinalysis) and serum creatine kinase (biochemistry) will be collected at Screening. In addition, myoglobin (urinalysis) and serum creatine kinase (biochemistry) may be collected at any

additional timepoints at the discretion of the investigator (including Day 97). A serum sample for blood alcohol level will be collected at all timepoints (includin Day 97). HbA1c will be collected at Screening and EOS/ETV Visit only.

[redacted]

[g] A videographer will record TETRAS administration at Screening.
[h] Washout of prestudy ET drug(s) except propranolol after the ICF was signed (Protocol Section 9.2.2.1) must be completed prior to Screening TETRAS assessment.
[i] Participants will be trained by study personnel on the use of software applications, IP diary, and devices necessary for the conduct of the study.
[j] Will be administered once daily, to be taken before bed, with a snack if bedtime is not within 2 hours of the evening meal. The 60-mg dose group will receive 15 mg SAGE-324 from Day 1 to Day 14, then 30 mg from Day 15 to Day 28, then 45 mg from Day 29 to Day 42, and then 60 mg from Day 43 to Day 90.
[k] A phone call to follow up on any AE(s) will be conducted, if deemed appropriate by the investigator, to review the current status of the participant.
[l] Including all medications and supplements taken within the 30 days prior to signing the ICF through the first dose of IP, as well as a complete history of all treatments for ET since the year of diagnosis.

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.
- If the medication start date is completely missing, do not impute a date, but consider it as a concomitant medication, unless the medication end date is before the initiation of treatment, in which case the medication will be considered prior.

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. SAS CODE FOR ANALYSIS OF PRIMARY EFFICACY ENDPOINT

Example code for MMRM:

The ODS statement is used to create output datasets, particularly COVB, for subsequent MCP Mod analysis.

```
Proc mixed data=[input dataset name]
           method=reml covtest alpha=0.05;
   Where CHG ne .;
   Class SUBJID TRTP(ref='Placebo') AVISITN;
   Model CHG = BASE TRTP AVISITN TRTP*AVISITN /
         htype=3
         ddfm=KENWARDROGER
         residual solution covb;
   Repeated AVISITN / sub=SUBJID type=[desired covariance structure];
   Lsmeans AVISITN * TRTP / cov pdiff cl alpha=0.05;
   ODS output
       solutionf=[output dataset name]
       covb=[output dataset name];
Run;
```

Example code for imputation of monotone missing data:

```
Proc mi data = [input dataset name]
        out  = monotone(rename=(_imputation_=impn))
        nimpute=20
        seed=XXXXXXX
        min   = . . 0 0 0 0 0 0 0 0
        max   = . . 24 24 24 24 24 24 24 24
        round = . . 1 1 1 1 1 1 1 1;
   Var trtpn base
       avisitn8 avisitn15 avisitn29 avisitn43
       avisitn57 avisitn71 avisitn91 avisitn97;
   MCMC impute=monotone chain=multiple;
   EM maxiter=500 converge=0.00001;
Run;
```

Example code for treatment-based imputation of non-monotone missing data:

```
Proc mi data=monotone
        out=imputed seed=XXXXXXX nimpute=1
        min   = . . 0 0 0 0 0 0 0 0
        max   = . . 24 24 24 24 24 24 24 24
        round = . . 1 1 1 1 1 1 1 1;
   By impn;
   Class trtpn;
   Var trtpn base
       avisitn8 avisitn15 avisitn29 avisitn43
       avisitn57 avisitn71 avisitn91 avisitn97;
```

```
   Monotone regression(/details);
Run;
```

APPENDIX D. LIST OF DISPLAYS

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14.1.2 *Analysis Sets (All Participants)*

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14.1.3.2 *Protocol Deviations Related to COVID-19 (Full Analysis Set)*

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14.1.5 *Summary of Disease History (Safety Analysis Set)*

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14.1.8.1 *Study Drug Exposure (Safety Analysis Set)*

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14.2.1.1 *Summary of Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale Item 4 (Upper Limb) Score (Full Analysis Set)*

14.2.1.2 *Change from Baseline in the Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale Item 4 (Upper Limb) Score – Mixed Effect Model for Repeated Measures (MMRM) (Full Analysis Set)*

14.2.1.3 *Change from Baseline in the Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale Item 4 (Upper Limb) Score – Sensitivity Analysis – Missing Data Imputation (Full Analysis Set)*

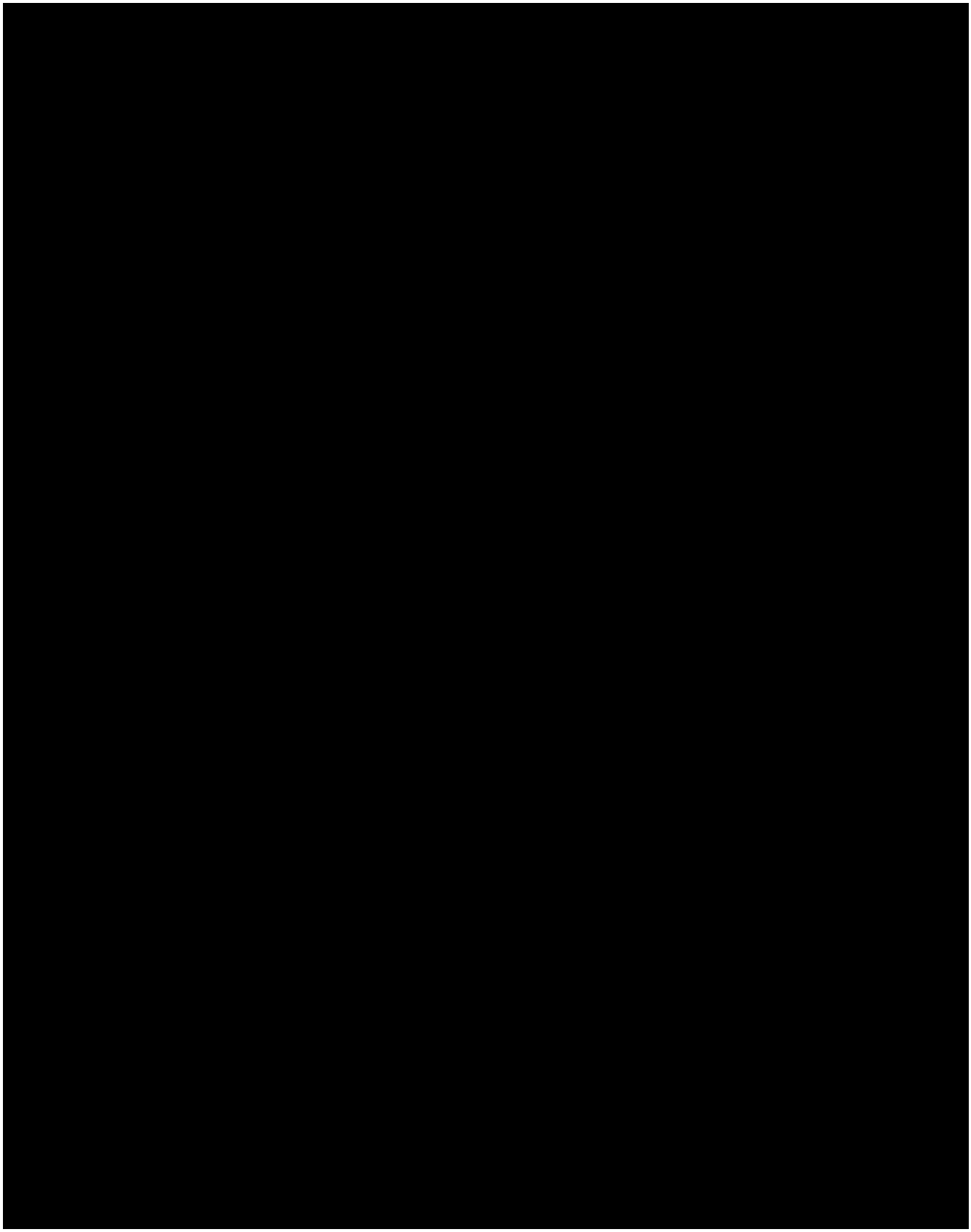
14.2.1.4 *MCP-Mod for Change from Baseline in the Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale Item 4 (Upper Limb) Total Score, Both (Full Analysis Set)*

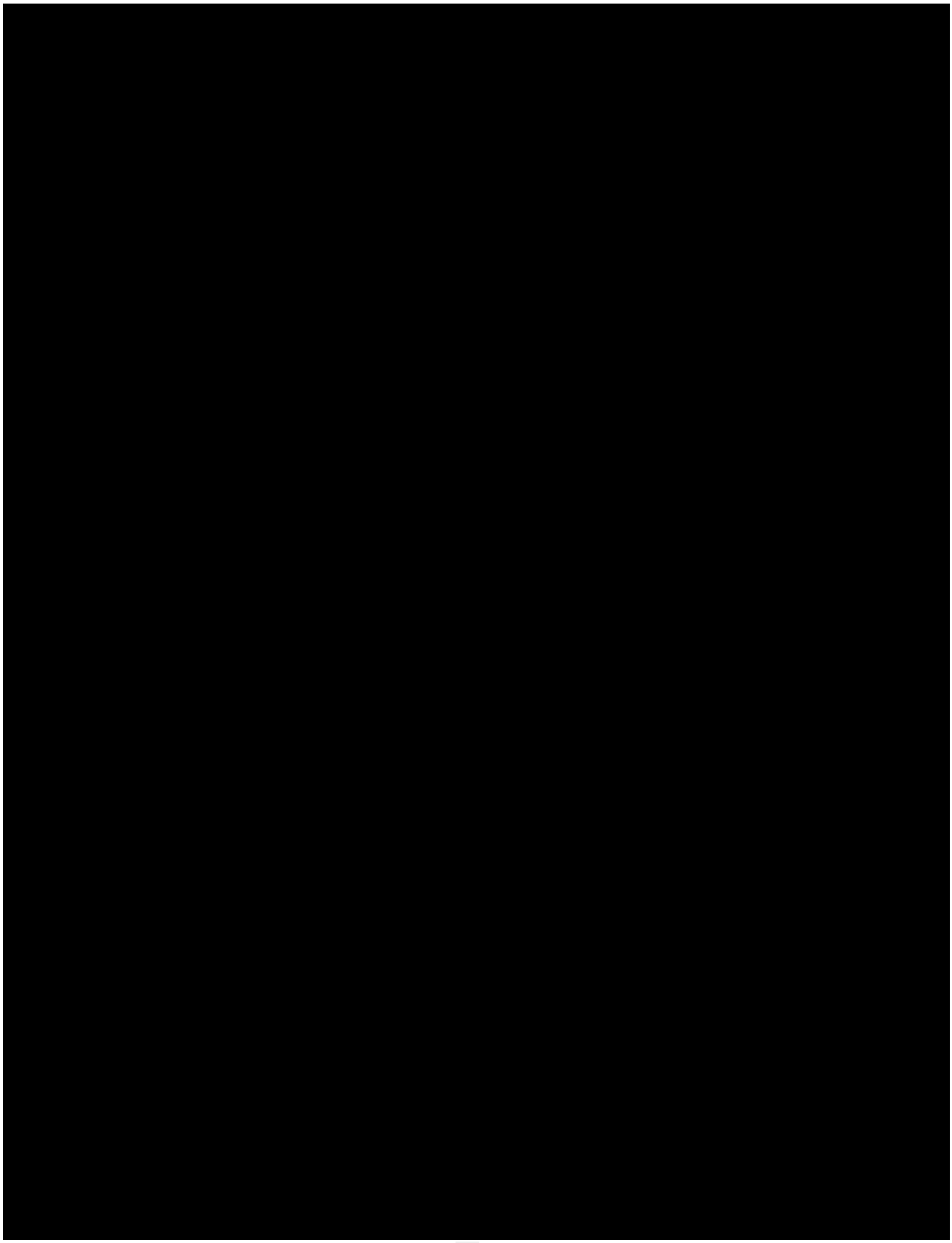
14.2.1.5 *Summary of Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale Item 4 (Upper Limb) Score (Per Protocol Set)*

14.2.1.6 *Change from Baseline in the Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale Item 4 (Upper Limb) Score – Mixed Effect Model for Repeated Measures (MMRM) (Per Protocol Set)*

14.2.1.7 *MCP-Mod for Change from Baseline in the Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale Item 4 (Upper Limb) Total Score, Both (Per Protocol Set)*

14.2.1.8 *Summary of Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale Item 4 (Upper Limb) Total Score by Subgroup (Full Analysis Set)*





14.3.1.1 *Summary of Treatment-Emergent Adverse Events (Safety Analysis Set)*

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14.3.1.3 *Treatment-Emergent Adverse Events by Preferred Term (Safety Analysis Set)*

14.3.1.4 *Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)*

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[redacted]

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[redacted]

[redacted]

16.2.7.1 Adverse Events

16.2.7.2 Serious Adverse Events (Safety Set)

16.2.7.3 Listing of Deaths (Safety Set)

16.2.7.4 Adverse Events Leading to Treatment Discontinuation (Safety Set)

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16.2.8.2.3 Drug Screen

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16.2.8.6 Mental Status Examination

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[redacted]

16.2.8.9 Phone Call During Treatment and Follow-up Period

[redacted]

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14.2.1.1.1 Least Squares Mean Change from Baseline in TETRAS Performance Subscale Item 4 (Upper Limb Tremor) Score by Time Point (Full Analysis Set)

14.2.1.1.2 Forest Plot of Change from Baseline in TETRAS Performance Subscale Item 4 (Upper Limb Tremor) Score at Day 91, Total Score (Full Analysis Set)

14.2.1.1.3 Dose Response for TETRAS Performance Subscale Item 4 (Upper Limb Tremor) Score at Day 91, Total Score (Full Analysis Set)

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sage_324-etd-202_sap_v1.0_20240617

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Status:	Signed
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