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9. STATISTICAL METHODS INTERIM ANALYSIS PLAN

Statistical Analysis Plan, version 1.0, dated 10 March 2021

STATISTICAL ANALYSIS PLAN
METHODS
PROTOCOL NUMBER 324-ETD-201

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

Author of SAP: [redacted]

Version: Version 1.0

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

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Sage Therapeutics, Inc

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1. LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this Statistical Analysis Plan.

Table 1: Abbreviations and Specialist Terms

Abbreviation	Definition
AE	adverse event
ADL	activities of daily living
AR(1)	Autoregressive (1)
ATC	anatomical therapeutic class
AUC_{inf}	area under the plasma concentration-time curve from time 0 to infinity
AUC_{0-t}	area under the plasma concentration-time curve from 0 to time t (last measurable concentration)
BLQ	below the limit of quantification
BMI	body mass index
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
C_{max}	maximum observed concentration
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End-of-Study
EOT	end of treatment
[redacted]	
ET	essential tremor
[redacted]	[redacted]
ETV	early termination visit
FAS	Full Analysis Set
ICF	informed consent form
IP	investigational product
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effects model for repeated measures
PCS	potentially clinically significant
[redacted]	[redacted]

Abbreviation	Definition
[redacted]	[redacted]
PT	preferred term
[redacted]	[redacted]
QTcF	QT corrected according to Fridericia's formula
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TETRAS	The Essential Tremor Rating Assessment Scale
T_{max}	time of occurrence of C_{max}
WHO-DD	World Health Organization Drug Dictionary

2. INTRODUCTION

This statistical analysis plan (SAP) is for the final analysis and is based on the approved clinical study protocol, Amendment 4, dated 15 December 2020, Version 5.

This SAP addresses the objectives of the study and describes the planned statistical analyses and data presentations, including the clinical pharmacology objective. 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 effect of SAGE-324 compared to placebo on upper limb tremor reduction in individuals with essential tremor (ET) after 28 days of treatment.

3.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the effect of SAGE-324 compared to placebo on overall upper limb tremor reduction
- To assess the effect of SAGE-324 compared to placebo on activities of daily living (ADLs)
- To assess the effect of SAGE-324 compared to placebo on overall tremor
- To evaluate the safety and tolerability of SAGE-324

4. STUDY ENDPOINTS

4.1. Efficacy Endpoint

4.1.1. Primary Efficacy Endpoint and Estimand

The primary efficacy endpoint of this study is the change from baseline compared to placebo in The Essential Tremor Rating Assessment (TETRAS) performance subscale part 4 upper limb tremor score on Day 29.

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

1. *There are two treatment regiments for participants to be evaluated: SAGE-324 or placebo.*
2. *The target population consists of participants age 18-80 years inclusive, with diagnosis of essential tremor of at least 3 years duration.*
3. *The outcome for the primary efficacy endpoint is mean change from baseline in clinic-based TETRAS performance subscale part 4 upper limb tremor score at Day 29.*
4. *The population-level summary measure is the difference in mean change from baseline in clinic-based TETRAS performance subscale part 4 upper limb tremor score of between the two groups (SAGE-324 and placebo).*

4.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are:

- Change from baseline compared to placebo in TETRAS performance subscale part 4 upper limb tremor score at all timepoints other than Day 29
- Change from baseline compared to placebo in Kinesia ONE accelerometer scores
- Change from baseline compared to placebo in the following:
    - TETRAS Scale ADL score
    - TETRAS Total Performance Score

[redacted]

4.2. Safety Endpoints

The safety endpoints of this study are:

- Incidence of treatment-emergent adverse events (TEAEs)

[redacted]

[redacted]

5. STUDY DESIGN

5.1. Overall Design

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

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

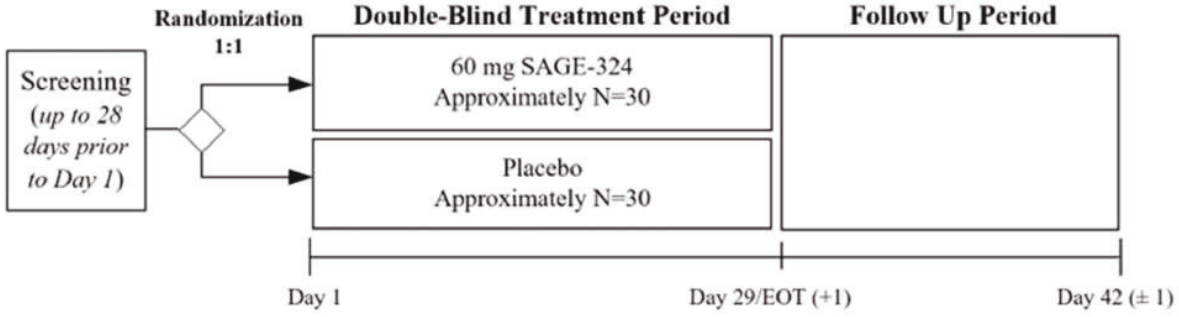
The Screening Period begins with the signing of the informed consent form (ICF). Eligible participants will visit the study center on Day 1 and complete additional eligibility assessments of safety and efficacy as specified in the Schedule of Assessments (Appendix A). Following completion of screening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

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

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

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

Figure 1: Study Design



Abbreviation: EOT = end of treatment

5.2. Sample Size and Power

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

5.3. Randomization

This is a randomized, double-blind, placebo-controlled study. Participants will be randomized in a 1:1 ratio to treatment groups (SAGE-324, 60 mg daily or placebo). Participants, site staff, and the sponsor will be blinded to treatment allocation.

Randomization schedules will be generated by an independent statistician. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding. The blinding of the study will be broken after the database has been locked.

5.4. Blinding and Unblinding

This is a randomized, double-blind, placebo-controlled study. Participants, site staff, and the sponsor will be blinded to treatment allocation. The randomization schedules will be kept strictly confidential, accessible only to authorized personnel until the time of unblinding after database lock.

During the study, the blind is to be broken only when the safety of a participant is at risk and the treatment plan is dependent on the study treatment received. Unless a participant is at immediate risk, the investigator should make diligent attempts to contact Sage prior to unblinding the study treatment administered to a participant. Requests from the investigator

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

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

If a participant or any study personnel become unblinded to treatment, the participant will be excluded from the Per Protocol analysis set.

6. MODIFICATIONS

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. This analysis set will be used for all listings and disposition.

7.2. Randomized Set

The Randomized Set will include all participants who are randomized.

7.3. Efficacy Analysis Set(s)

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

The Per Protocol Set will include all participants in the Full Analysis Set without any major protocol deviations that could affect efficacy. The review of major protocol deviations will be completed, and the decision on whether the deviation affects efficacy will be documented before database unblinding. Note that a positive cotinine test on Days 1, 8, 15, 22, or 29 constitutes a major protocol deviation and excludes the participant from the Per Protocol Set. In addition, the Per Protocol Set will exclude full analysis set participants satisfying any of the following conditions:

1. Study Drug Adherence (defined in Section 8.2.7) < 75%
2. 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

7.4. Safety Analysis Set

The Safety Set will include all participants administered IP.

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

Unless otherwise specified, continuous endpoints will be summarized with n, mean, standard deviation (SD), median, 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.

Categorical variables (eg, presence 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 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 the number of participants who were screened, 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 Set). Percentages will be calculated based on the participants randomized and dosed. These data will be provided by randomized treatment groups. 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 the randomized treatment.

A completer for the study is defined as one who completed the final follow-up 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 is taken on Day 28, and is derived from the End of Treatment CRF page with completion question answered No. The main reason is provided in the same CRF page.

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.

8.2.2. Protocol Deviations

Protocol deviations will be captured on 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 actual treatment received using Safety Set. The minor deviations will be included in the listing. The Covid-19 related protocol deviations will also be summarized. 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.

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 hand) will be summarized with descriptive statistics by treatment using the Safety Set.

Baseline subgroups will be summarized for the following categories:

- Race (Black or African American, White, Other)
- Sex (Female, Male)
- Age (<65, 65-80 years)
- BMI (<18.5, 18.5 - <25, 25 - <30, ≥30 kg/m2)

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 22.1, September 2019, 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 Set.

Medical history related to ET (including age at diagnosis, age at onset of ET, whether alcohol helps participant tremor, 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 subgroup will be summarized for the following categories:

- Age at essential tremor diagnosis (< 40 years, 40-60 years, >60 years)
- Age participant thinks essential tremor started (< 40 years, 40-60 years, >60 years)
- Years with essential tremor diagnosis (3-<6 years, 6-10 years, >10 years)
- Years since participant thinks essential tremor started (3-<6 years, 6-10 years, >10 years)
- Alcohol helps tremor: Yes (Intermediate, Worked Well), No (No, a little), NA
- Past treatment for essential tremor (Yes/No)

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 2019, 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); all psychotropic medications taken in the 30 days prior to screening will also be recorded. Those medications taken prior to the initiation of the investigational product will be denoted “Prior”. Those medications taken prior to the initiation of the investigational product and continuing beyond the initiation of the investigational product or those medications started at the same time or after the initiation of the investigational product will be denoted “Concomitant”. Note that medication taken before the initial dosing of investigational product 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.

Details of prior and concomitant medications will be listed by participant, start date, and verbatim term. Prior and concomitant medications will be summarized separately for the Safety Set as the number and percentage of participants with each medication at both the ATC and PT levels.

8.2.6. Investigational Product Exposure

Total drug exposure (in mg) is defined as the total investigational product 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 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 investigational product (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.

Percent of the planned exposure received is defined as the total drug exposure, divided by planned exposure, times 100. For participants who complete the treatment period, planned exposure is 28 days of treatment planned, times 60 mg for participants randomized to SAGE-324. For participants who discontinue the treatment early, planned exposure is the total exposure duration times 60 mg for participants randomized to SAGE-324. For participants randomized to placebo, this measure is not applicable.

Total drug exposure, total exposure duration, and percent of the planned exposure received will be summarized using the Safety Set and randomized treatment group. Also, the number and percentage of participants with <80%, 80%-<100%, and 100% of full 60mg dose (4 tablets every day) consumed will be summarized.

8.2.7. Study Drug Adherence

Study drug adherence (%) is defined as the number of tablets taken, divided by the number of tablets planned to be taken, times 100.

The schedule of study drug is 4 tablets of a 15mg strength with a total of 60mg per day, but the investigator may reduce the dose of IP from 60 mg in 15 mg decrements (ie, 60, to 45, to 30 mg). The number of planned tablets intake is defined as follows:

1. If the participant does not have any dose reduction and completes the planned 28 days of treatment, the planned number of tablets is 4*28
2. If the participant does not have any dose reduction, but discontinues the study drug early, the planned number of tablets is 4*(Date of last dose – date of first dose + 1)
3. If the participant ever has a dose reduction, the planned number of tablets is:

   4*(date of last dose on 60mg or equivalent placebo dose - date of first dose on 60mg or equivalent placebo dose +1)

   + 3*(date of last dose on 45mg or equivalent placebo dose - date of first dose on 45mg or equivalent placebo dose +1)

   + 2*(date of last dose on 30mg or equivalent placebo dose - date of first dose on 30mg or equivalent placebo dose +1).

   If the participant does not have dose reduction to 30mg or equivalent placebo dose, the last term is 0.

Study drug adherence will be summarized descriptively using the Full Analysis Set. Number and percentage of participants with study drug adherence in categories <75%, 75-100%, >100% will be provided.

8.3. Efficacy Analysis

8.3.1. Definition of Efficacy Variable(s)

8.3.1.1. Primary Efficacy Assessment

The Essential Tremor Rating Assessment (TETRAS) Performance Subscale Part 4 upper limb tremor score will be assessed at each clinic visit as specified in the Schedule of Assessments (Appendix A).

For the Performance Subscale Part 4 upper limb tremor score, all 3 maneuvers in the upper limb assessments of Part 4 (Subscale Items 4a, 4b, and 4c) will be completed for both arms, first for the left arm and then for the right. The Part 4 subscale ordinally rates postural (limbs extended forward maneuver, wing-beating [elbows flexed] maneuver), and kinetic (finger-nose-finger maneuver) tremor on a 0 to 4 severity scale in 0.5-point increments, with higher scores indicating more severe tremor. The overall Performance Subscale Part 4 upper limb tremor score range for a given side (left or right) is 0 to 12, and for both sides combined is 0 to 24.

The primary efficacy assessment is the change from baseline compared to placebo in TETRAS Performance Subscale Part 4 upper limb tremor total score for both sides combined at Day 29 based on the Full Analysis Set.

8.3.1.2. Secondary Efficacy Assessments

The secondary efficacy assessments include the TETRAS Performance Subscale Part 4 upper limb tremor score at timepoints other than Day 29 (see Section 8.3.1.1), and the Kinesia ONE™ accelerometer score, TETRAS Scale ADL score, and TETRAS total performance score at all visits.

8.3.1.2.1. Kinesia ONE™ Accelerometer Score

Kinesia ONE™ is an ISO-certified wireless motion sensor worn distally on the index finger, which utilizes 3 orthogonal accelerometers and 3 orthogonal gyroscopes to monitor three-dimensional motion. Via the Kinesia ONE™ software application, measures of three-dimensional motion are converted to scores ranging from 0 to 4, per assessed maneuver on a given side; higher scores indicate greater tremor severity. Motion in both arms is captured.

For this study, the forward outstretched postural tremor, lateral “wing beating” postural tremor, and kinetic tremor will be measured for left, right, and both sides. The total score on a given side is the sum of the three individual scores for the side, thus the total score for a given side ranges from 0 to 12; the total score for both sides ranges from 0 to 24.

The secondary efficacy assessments include the change from baseline compared to placebo in Kinesia ONE accelerometer scores at all visits.

8.3.1.2.2. Essential Tremor Rating Assessment Scale

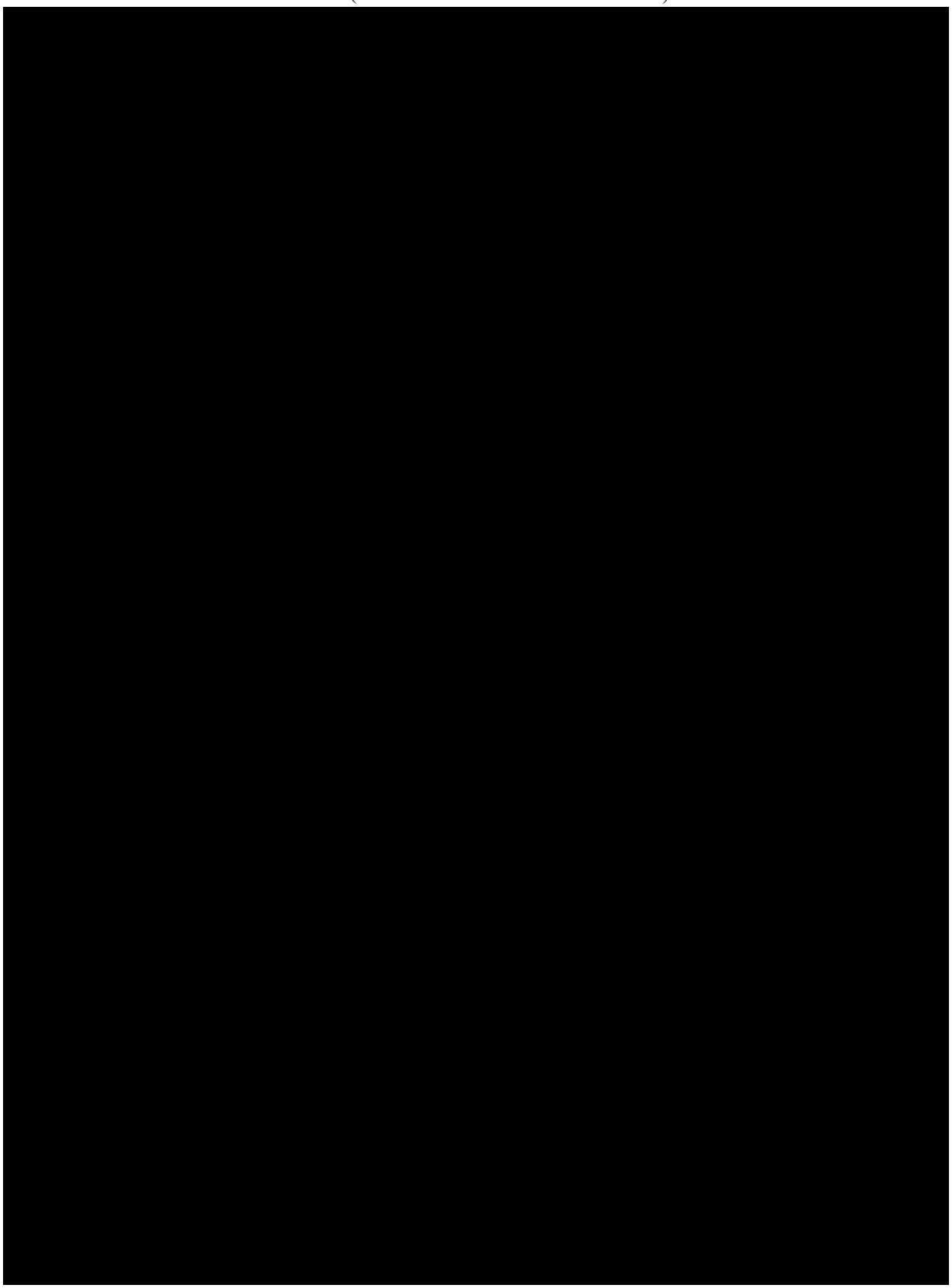
Three different components of TETRAS will be assessed in this study. The TETRAS ADL subscale, total performance score, and performance subscale part 4 upper limb tremor score will each be separately assessed at each clinic visit as specified in the Schedule of Assessments (Appendix A).

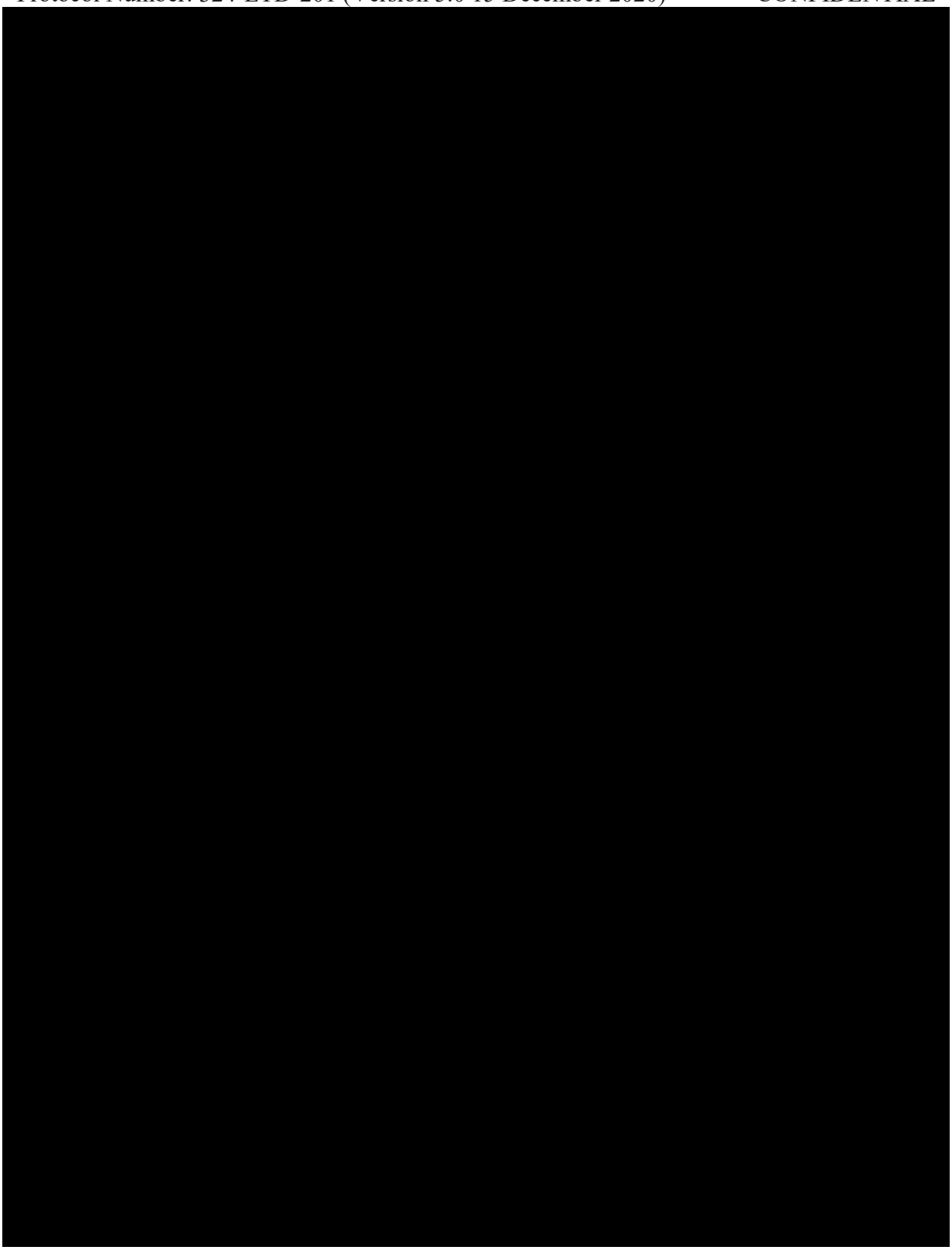
For details on the TETRAS performance subscale part 4 upper limb tremor score, see Section 8.3.1.1.

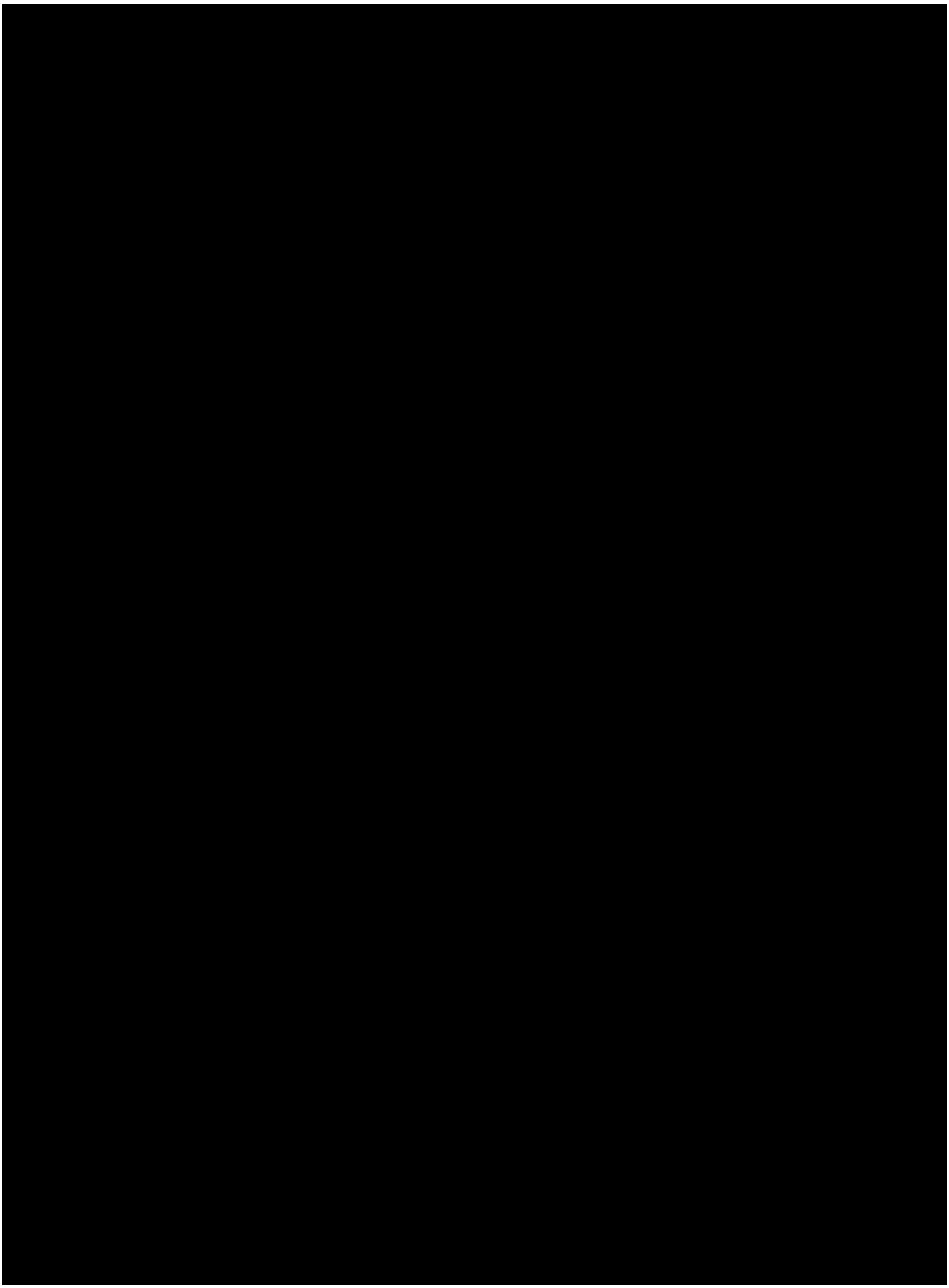
The ADL subscale assesses how ET is impacting typical activities of daily living (ie, speech, eating, drinking, dressing, personal hygiene, writing, occupational impairment, social impact, and activities affected by upper limb tremor). It consists of 12 items that are each rated on a scale from 0 (normal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

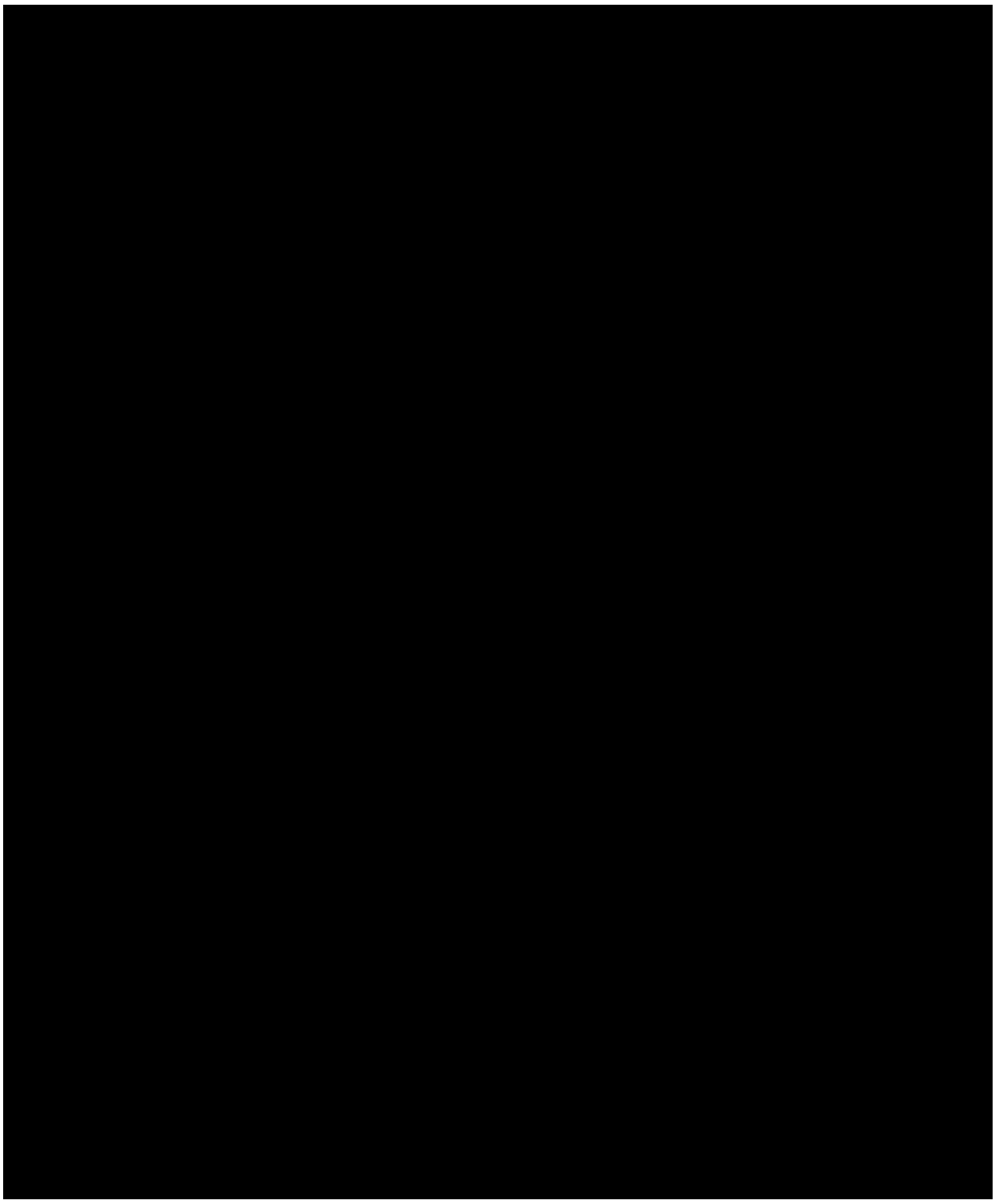
The total performance score is based on overall rating of tremor amplitude in the voice, limbs, head, face, trunk, and also measures functional task capabilities, ie, handwriting, spirograph, and holding a pen over a dot. Each of these items is rated on a scale from 0 (no tremor) to 4 (severe tremor).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

The secondary efficacy assessments include the change from baseline compared to placebo in the TETRAS scale ADL score and TETRAS total performance score at all visits and the TETRAS performance subscale part 4 upper limb tremor score at all visits other than Day 29.









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 period visits (Day 1, Day 8, Day 22 and Day 29). Post-treatment visits (Day 42), as well as the unscheduled, end-of-treatment (EOT), and early termination (ET) visits, 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 below. The mapping will follow the visit window in Table 2. In order 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 displays visit windows for efficacy analysis.

Table 2: Visit Windows for Efficacy Analysis

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Screening	Day -1	Days -28- 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	Day 12 to 18
Day 22 (±1 day)	22	Day 19 to 25
Day 29 (+1 day)	29	Day 26 to 30
Day 42 (±1 day)	42	>=Day 31

Once analysis visits are assigned based on the visit windows, all visits, including scheduled visits, unscheduled visits, and EOT/ET 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. 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 45) will remain in the database and will be included in the listings.

For assessments scheduled only at Day 1, Day 29/EOT and Day 42/EOS, [redacted] the following visit windows are used.

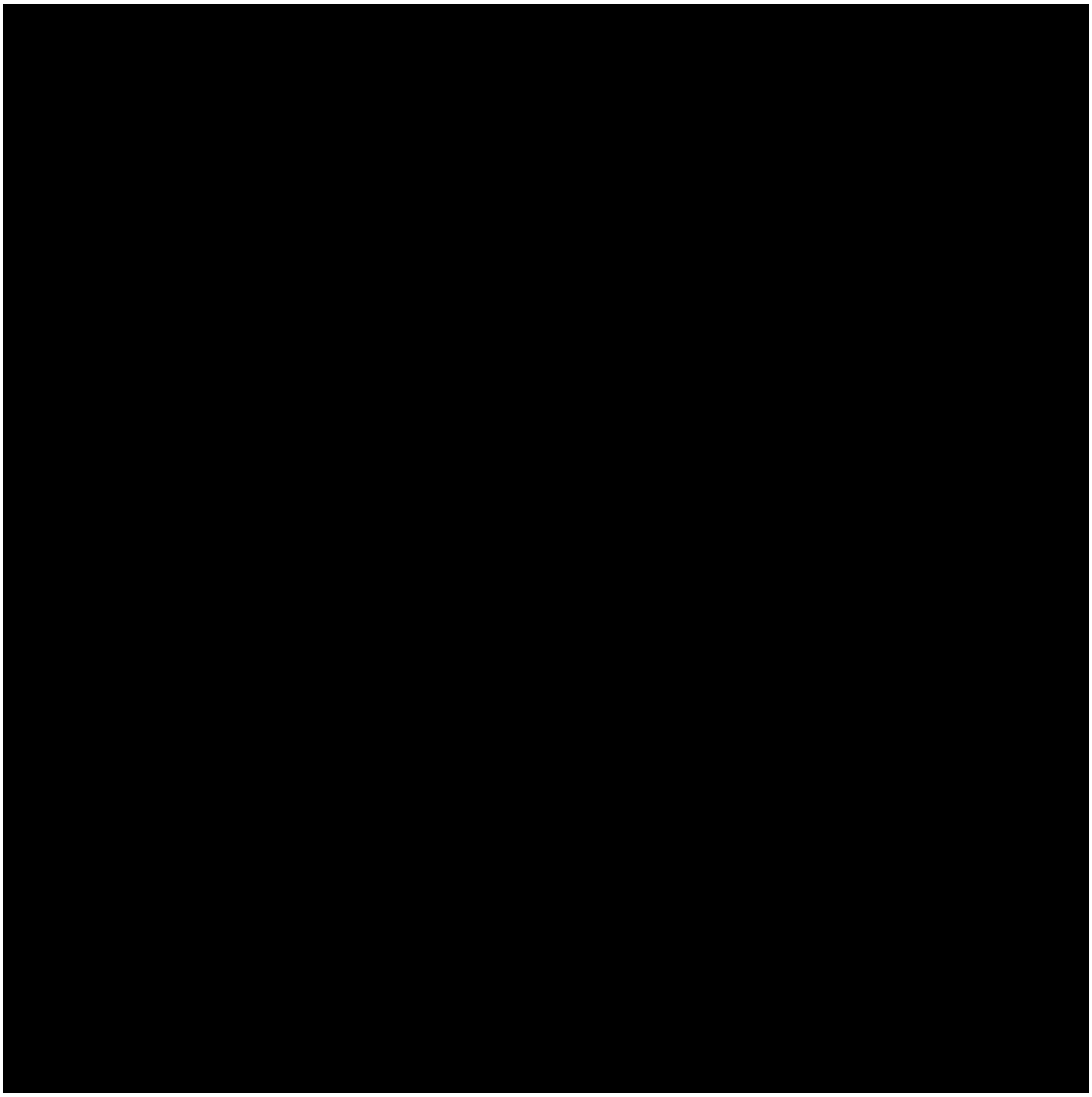
Table 3: Visit Windows for Other Efficacy Analysis

Scheduled Visit	Study Day of Expected Visit	Study Day Window for Visit
Day 1	Day 1	Day 1
Day 29 (+1 day)	29	Day 2 to 30
Day 42 (±1 day)	42	>=Day 31

8.3.3. Analysis of Efficacy Variable(s)

The efficacy analysis uses the Full Analysis Set and presents data by randomized treatment, unless specified otherwise. The following efficacy endpoints will be summarized descriptively by randomized treatment at each scheduled time point:

- TETRAS performance subscale part 4 upper limb tremor scores (individual and total score by side and combined) – observed, change from baseline, percent change from baseline
- Kinesia ONE accelerometer scores – observed, change from baseline, percent change from baseline
- TETRAS performance total score – observed, change from baseline, percent change from baseline
- TETRAS ADL score - observed, change from baseline, percent change from baseline



The TETRAS performance subscale part 4 upper limb tremor change from baseline total score, TETRAS performance total score, TETRAS performance subscale Part 4/6/7/8 score, and TETRAS ADL score will also be presented by the following subgroups:

- Age group: <65, 65-80 years
- Sex: Male, Female
- Race: White, Black or African American, Other
- BMI (<18.5, 18.5-<25, 25-<30, ≥30 kg/m2)
- Age at essential tremor diagnoses (< 40 years, 40-60, >60 years)
- Age participant thinks essential tremor started (< 40 years, 40-60, >60 years)
- Years with essential tremor diagnosis (3-<6 years, 6-10 years, >10 years)
- Years since participant thinks essential tremor started (3-<6 years, 6-10 years, >10 years)
- Alcohol helps tremor: Yes (Intermediate, Worked Well), No (No, a little), NA
- Baseline TETRAS performance subscale part 4 upper limb tremor score (<12, ≥12)

8.3.3.1. Mixed Effects Model for Repeated Measures

8.3.3.1.1. Analysis of Primary Efficacy Variable

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

5. *There are two treatment regiments for participants to be evaluated: SAGE-324 or placebo.*
6. *The target population consists of participants age 18-80 years inclusive, with diagnosis of essential tremor of at least 3 years duration.*
7. *The outcome for the primary efficacy endpoint is mean change from baseline in clinic-based TETRAS performance subscale part 4 upper limb tremor score at Day 29.*
8. *The population-level summary measure is the difference in mean change from baseline in clinic-based TETRAS performance subscale part 4 upper limb tremor score of between the two groups (SAGE-324 and placebo).*

This will be analyzed using a mixed effects model for repeated measures (MMRM); the model will include treatment, baseline TETRAS performance subscale part 4 upper limb tremor score, assessment timepoint, and timepoint-by-treatment as explanatory variables. All

explanatory variables will be treated as fixed effects. All postbaseline clinic visits will be included in the model. The main comparison will be between SAGE-324 and placebo at the 29-day timepoint. Model-based point estimates (ie, least squares means, 95% confidence intervals, and p-values) will be reported where applicable. An unstructured covariance structure will be used to model the within-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. If the model still does not converge with AR(1) structure, no results will be reported. When the covariance structure is not unstructured, the sandwich estimator for the variance covariance matrix will be derived, using the EMPIRICAL option in the PROC MIXED statement in SAS.

For each model, the comparison of interest will be between SAGE-324 and matching placebo at Day 29 time point, with model-based point estimates (i.e., LS means), 95% confidence intervals, and p-values will be reported for all time points.

8.3.3.1.2. Analysis of Secondary Efficacy Variables

Similar to those methods described above for the primary endpoint, a MMRM will be used for the analysis of the change from baseline in other time points in TETRAS performance subscale part 4 upper limb tremor scores at all other visits/time points, TETRAS total performance scores, TETRAS ADL scores, and Kinesia ONE accelerometer scores, including total score and each individual item by side and combined total score. A MMRM will also be used for the analysis of the change from baseline in TETRAS performance subscale part 4 upper limb/part 6 (Archimedes sprirals)/part 7(Handwriting)/part 8 (Dot approximation task) combined score.

Line plots of model-based LS Means and standard errors (SE) over time will be prepared for change from baseline in TETRAS performance subscale part 4 upper limb tremor total score (by side and combined), TETRAS performance total score, TETRAS performance subscale part 4/6/7/8 combined score, TETRAS ADL total score, and Kinesia ONE accelerometer total score (by side and combined).

8.3.3.1.3. Sensitivity Analysis of Primary Endpoint

The following sensitivity analysis of the primary endpoint will be performed to assess the robustness of the primary analysis. For participants who terminate from treatment prior to the end of the analysis period for any of the following reasons: adverse event, noncompliance with study procedures, death, physician decision, or requires prohibited medication, missing measurements will be imputed as the worst post-baseline observation; for all other participants having missing measurements, missing values will be imputed with the last non-missing value before the scheduled visit time (LOCF principle).

If any of the sensitivity analyses yields a result that is in a different direction from the result of the primary analysis, the nature of the discrepancy will be examined to clearly explain the

discrepancy based on statistical principles and the discrepancy will be discussed in the clinical study report.

Another sensitivity analysis of primary endpoint will be performed to exclude the patients from the sites with potential risk of unblinding due to kit information accessed/downloaded, which is listed below:

8.3.3.1.4. Supportive Analysis of Primary and Secondary Endpoints

Summary of TETRAS performance subscale part 4 upper limb tremor total score (by side and combined), TETRAS performance total score, TETRAS performance subscale part 4/6/7/8 score, TETRAS ADL total score, and Kinesia ONE accelerometer total scores (by side and combined) along with model-based estimates and line plot will be provided for Per Protocol Set as a supportive analysis for the primary and secondary endpoint.

8.3.3.1.5. Subgroup Analyses of Primary and Key Secondary Endpoints

The TETRAS performance subscale part 4 upper limb tremor change from baseline total score (by side and combined), TETRAS performance total score, TETRAS performance subscale Part 4/6/7/8 score, and TETRAS ADL score will also be presented by the following subgroups:

- Age group: <65, 65-80 years
- Sex: Male, Female
- Race: White, Black or African American, Other
- BMI: <18.5, 18.5 - <25, 25-< 30, ≥30 kg/m2
- Age at essential tremor diagnoses: <40 years, 40-60 years, >60 years

- Age participant thinks essential tremor started: <40 years, 40-60 years, >60 years
- Years with essential tremor diagnosis: 3-<6 years, 6-10 years, and >10 years
- Years since participant thinks essential tremor started: 3-<6 years, 6-10 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: <12, >=12

If any of the subcategories has <5 patients fall into that category, that category should be combined with the next adjacent category with smaller counts. For example, if the number of patients fall into BMI category <18.5 is <5, this category should be combined with the 18.5 - <25 group.

Forest plots for subgroup analysis for change from baseline in TETRAS performance subscale part 4 upper limb tremor total score (by side and combined), TETRAS performance total score, TETRAS performance subscale Part 4/6/7/8 score, and TETRAS ADL total score at Day 29 – LS means, confidence interval – will be provided.

[redacted]

8.4. Safety Analysis

Safety and tolerability of SAGE-324 will be evaluated by adverse events, [redacted] Safety data will be listed by participant and summarized by treatment group.

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 **Error! Reference source not found.**.

All safety summaries will be performed on the Safety Set using treatment received. See Table 4 for details on how safety endpoints will be presented.

No statistical hypothesis testing will be conducted on the safety data.

Table 4: Presentation of Safety Endpoints

Safety Evaluation	Incidence	Raw Value	Change from Baseline	Clinical Significance	Abnormality	Derived PCS values
AEs	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 22.1 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. The term IP includes both SAGE-324 and placebo. Summary tables of AEs will include TEAEs only.

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

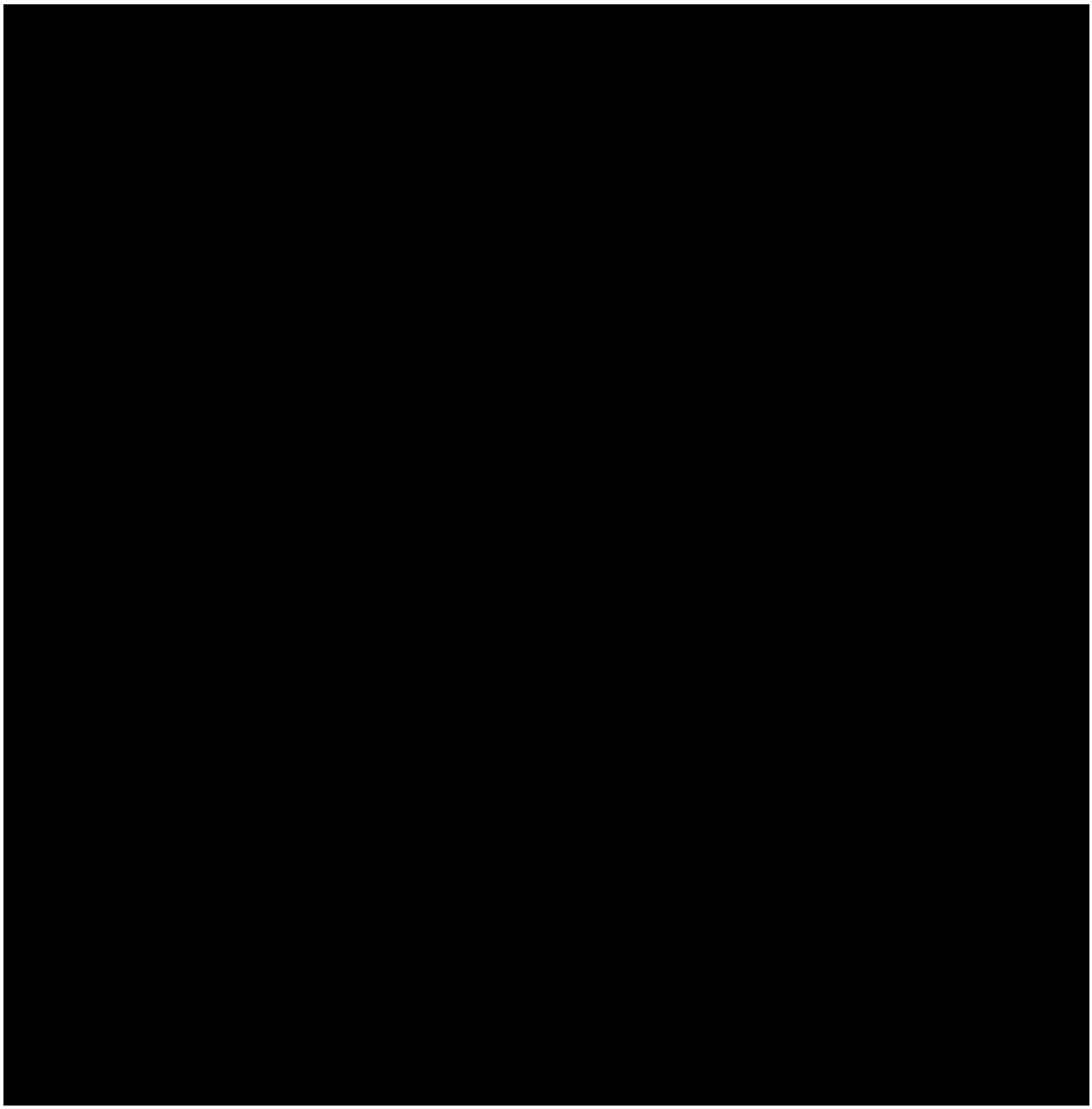
- TEAE
- Maximum severity of TEAE (mild TEAE, moderate TEAE, severe TEAE)
- TEAE leading to study treatment discontinuation
- TEAE leading to study discontinuation
- Serious TEAE
- Serious TEAE leading to study treatment discontinuation
- Serious TEAE leading to study discontinuation
- TEAE resulting in death

The incidence of TEAEs will be summarized by System Organ Class (SOC) and 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 serious adverse events (SAEs) will also be summarized, sorted by descending frequency in SOC and PT within the SAGE-324 group.

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 only within the SAGE-324 group.

All AEs and SAEs (including those with onset or worsening before the start of investigational product) 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.

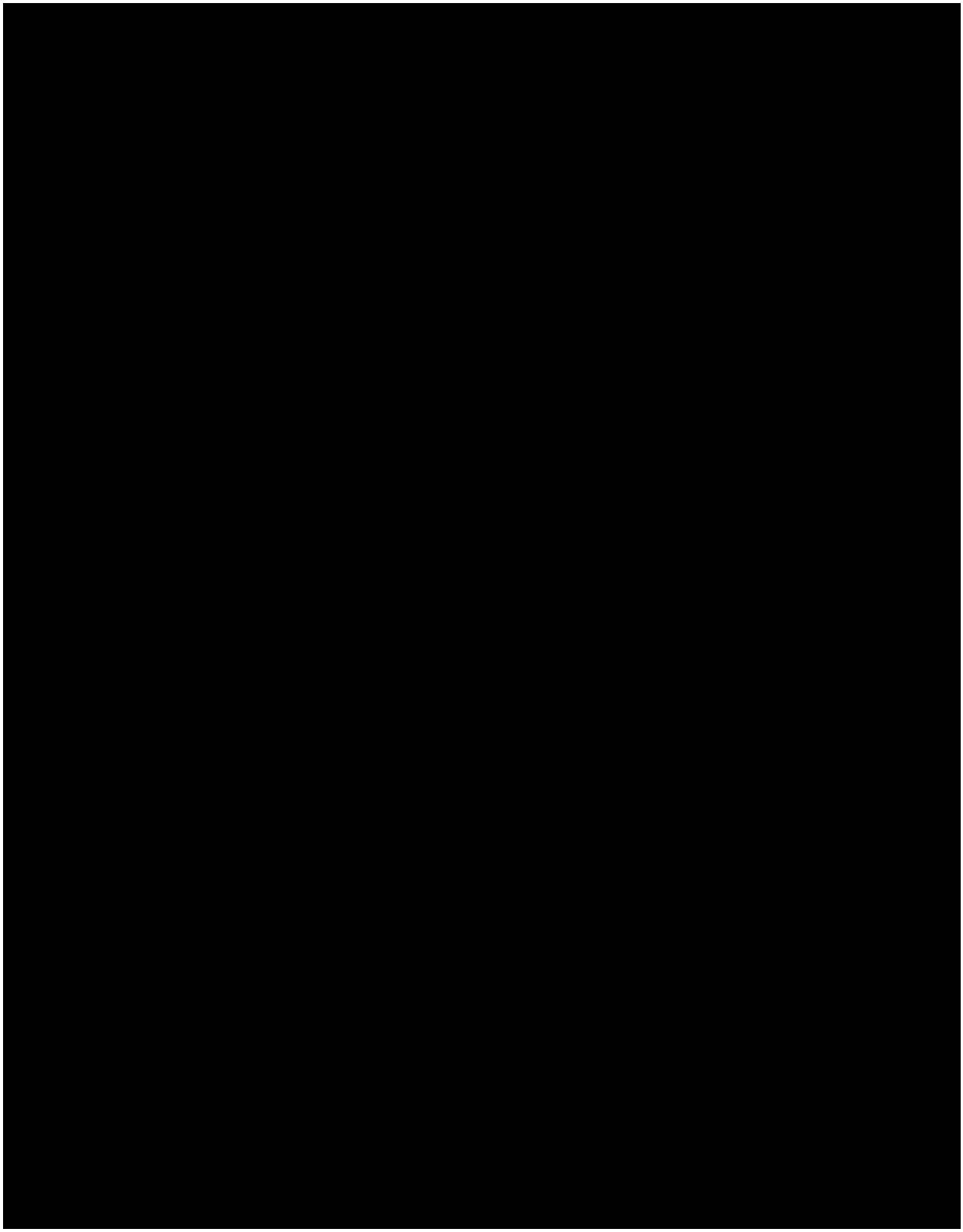


[redacted]

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]



[redacted]

8.6. Other Patient-Reported Assessments

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

This questionnaire will be analyzed as post-hoc.

8.7. Other Analysis

Not applicable.

9. SUMMARY OF INTERIM AND DMC ANALYSES

9.1. Interim Analysis

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

9.2. DMC Analysis

Not applicable.

10. REFERENCES

11. LIST OF APPENDICES

Appendix A: Schedule of Assessments

Appendix B: Handling of Missing Dates

Appendix C: List of Displays

[redacted]

APPENDIX A. SCHEDULE OF ASSESSMENTS

Schedule of Assessments

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

Assessment	**Screening**	**Treatment Period**									**Follow-up Period**	
Study Day	**-28 to -1**	**1**	**5 (±1) Phone Call**	**8 (±1)**	**12 (±1) Phone Call**	**15 (±1)**	**19 (±1) Phone Call**	**22 (±1)**	**26 (±1) Phone Call**	**29 (+1) EOT**	**35 (±1) Safety Phone Call**	**42 (±1) EOS/ ETV[a]**
Body height	X											
Body weight	X											
Vital signs[c]	X	X		X		X		X		X		X
12-Lead ECG[d]	X	X		X		X		X		X		X
Chemistry/hematology/ coagulation/urinalysis	X	X		X		X		X		X		X
[redacted]												
Kinesia[f]	X	X		X		X		X		X		X
TETRAS[g]	X	X		X		X		X		X		X
[redacted]												

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

Abbreviations: ADL = activities of daily living; AE = adverse event; [redacted]; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; [redacted] ETV = early termination visit; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; ICF = informed consent form; min = minutes; IP = investigational product; MSE = mental state examination; [redacted]

[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, Kinesia, ECG, blood sample collection for [redacted] clinical laboratory assessments, and questionnaires.
- All assessments will be performed predose unless specified in a footnote.

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

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

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

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

[f] [redacted]

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

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

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

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 at 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 subject is missing a treatment start date, medication will not be classified as either prior or concomitant.

APPENDIX C. LIST OF DISPLAYS

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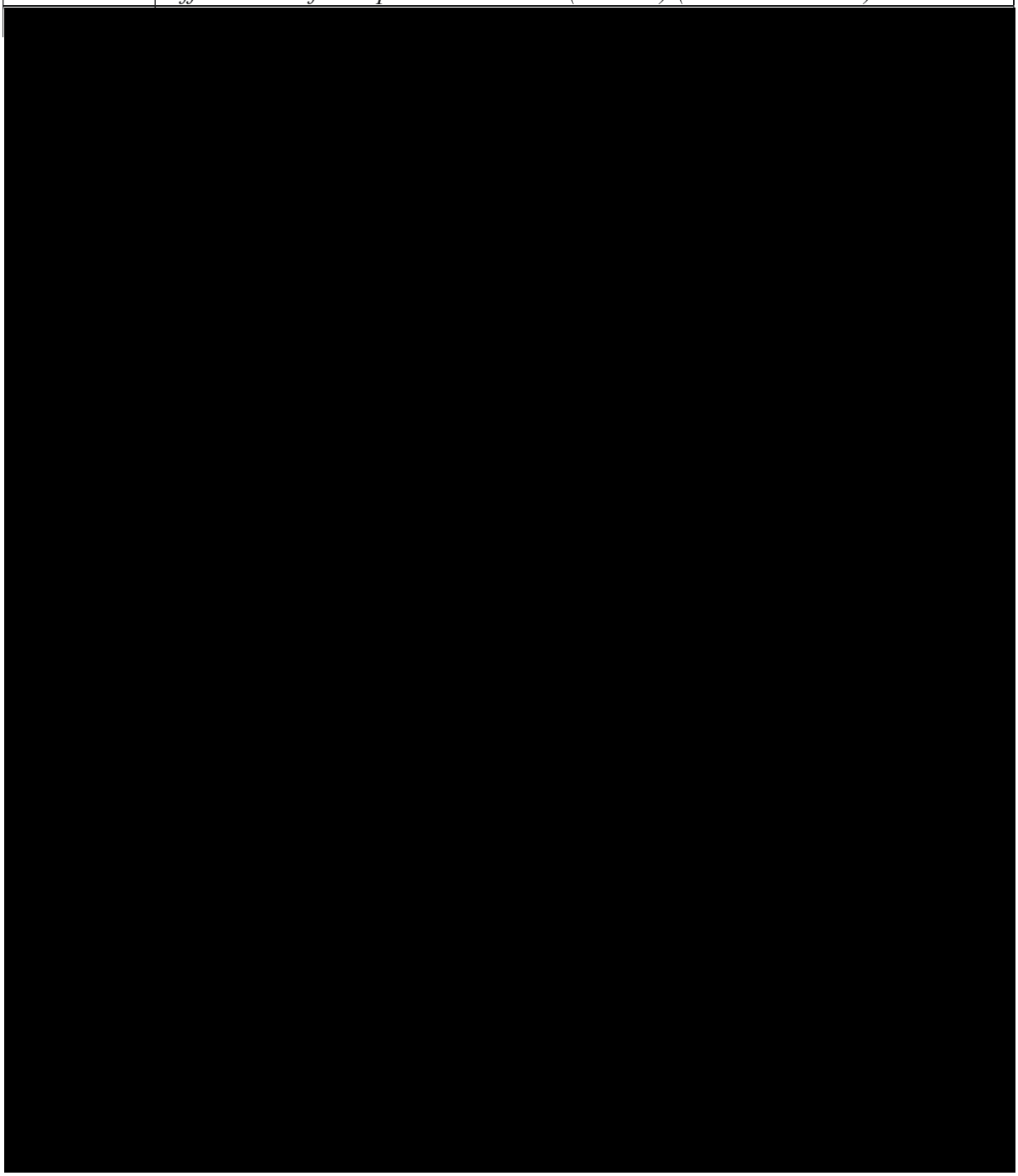

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[redacted]

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[redacted]

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[redacted]

14.3.4.4.1.1	*Summary of Urinalysis, Continuous Parameters (Safety Set)*
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[redacted]

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[redacted]	
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[redacted]	

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16.2.5.1	*Study Drug Dispensation and Return*
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[redacted]	[redacted]
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16.2.6.2	*Kinesia ONE™ Accelerometer Score*
[redacted]	

[redacted]	[redacted]
16.2.7.1	*Adverse Events*
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16.2.8.4	*Vital Signs*
16.2.8.5	*Physical Examinations*
16.2.8.6	*Mental Status Examination*
16.2.8.7	*Abbreviated Neurological Examination*
[redacted]	[redacted]
16.2.8.9	*Phone Call During Treatment and Follow-up Period*
[redacted]	[redacted]
[redacted]	[redacted]

Figures

14.2.1.1.1	*Least Squares Mean Change from Baseline in TETRAS Performance Subscale Part 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 Part 4 Upper Limb Tremor Score at Day 29, Total Score (Full Analysis Set)*
14.2.1.2	*Least Squares Mean Change from Baseline in TETRAS Performance Subscale Part 4 Upper Limb Tremor Score by Time Point (Per Protocol Set)*
14.2.2.1.1	*Least Squares Mean Change from Baseline in TETRAS ADL Score by Time Point (Full Analysis Set)*
14.2.2.1.2	*Forest Plot of Change from Baseline in TETRAS ADL Score at Day 29, Total Score (Full Analysis Set)*
14.2.2.2	*Least Squares Mean Change from Baseline in TETRAS ADL Score by Time Point (Per Protocol Set)*
14.2.3.1.1	*Least Squares Mean Change from Baseline in TETRAS Total Performance Score by Time Point (Full Analysis Set)*
14.2.3.1.2	*Forest Plot of Change from Baseline in TETRAS Total Performance Score at Day 29, Total Score (Full Analysis Set)*
14.2.3.2	*Least Squares Mean Change from Baseline in TETRAS Total Performance Score by Time Point (Per Protocol Set)*
14.2.3.3.1	*Least Squares Mean Change from Baseline in TETRAS Performance Subscale Part 4/6/7/8 Score by Time Point (Full Analysis Set)*
14.2.3.3.2	*Forest Plot of Change from Baseline in TETRAS Performance Subscale Part 4/6/7/8 Score at Day 29 (Full Analysis Set)*

14.2.3.4	*Least Squares Mean Change from Baseline in TETRAS Performance Subscale Part 4/6/7/8 Score by Time Point (Per Protocol Set)*
14.2.4.1	*Least Squares Mean Change from Baseline in Kinesia™ Accelerometer Upper Limb Total Score by Time Point (Full Analysis Set)*
14.2.4.2	*Least Squares Mean Change from Baseline in Kinesia™ Accelerometer Upper Limb Total Score by Time Point (Per Protocol Set)*

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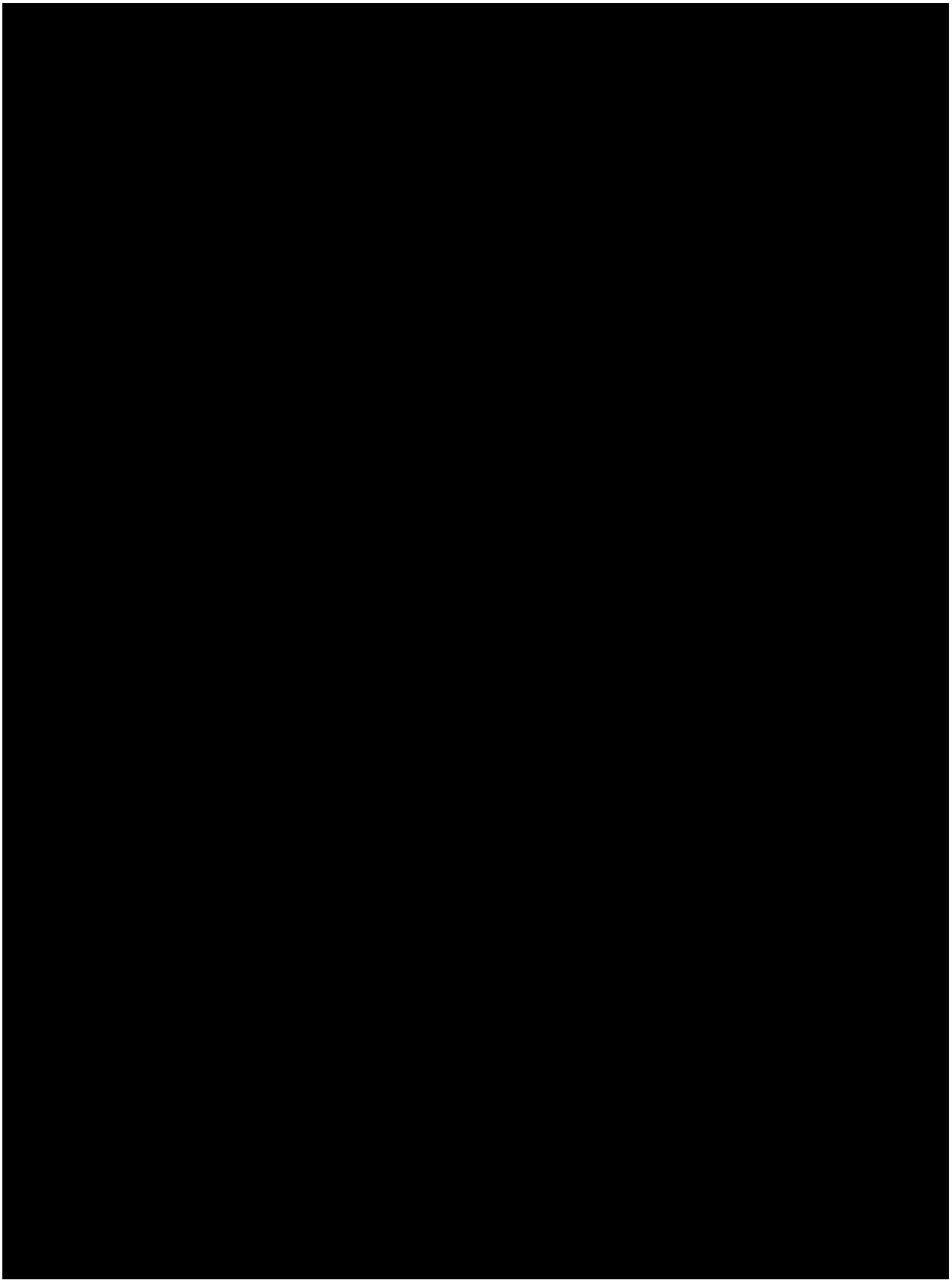

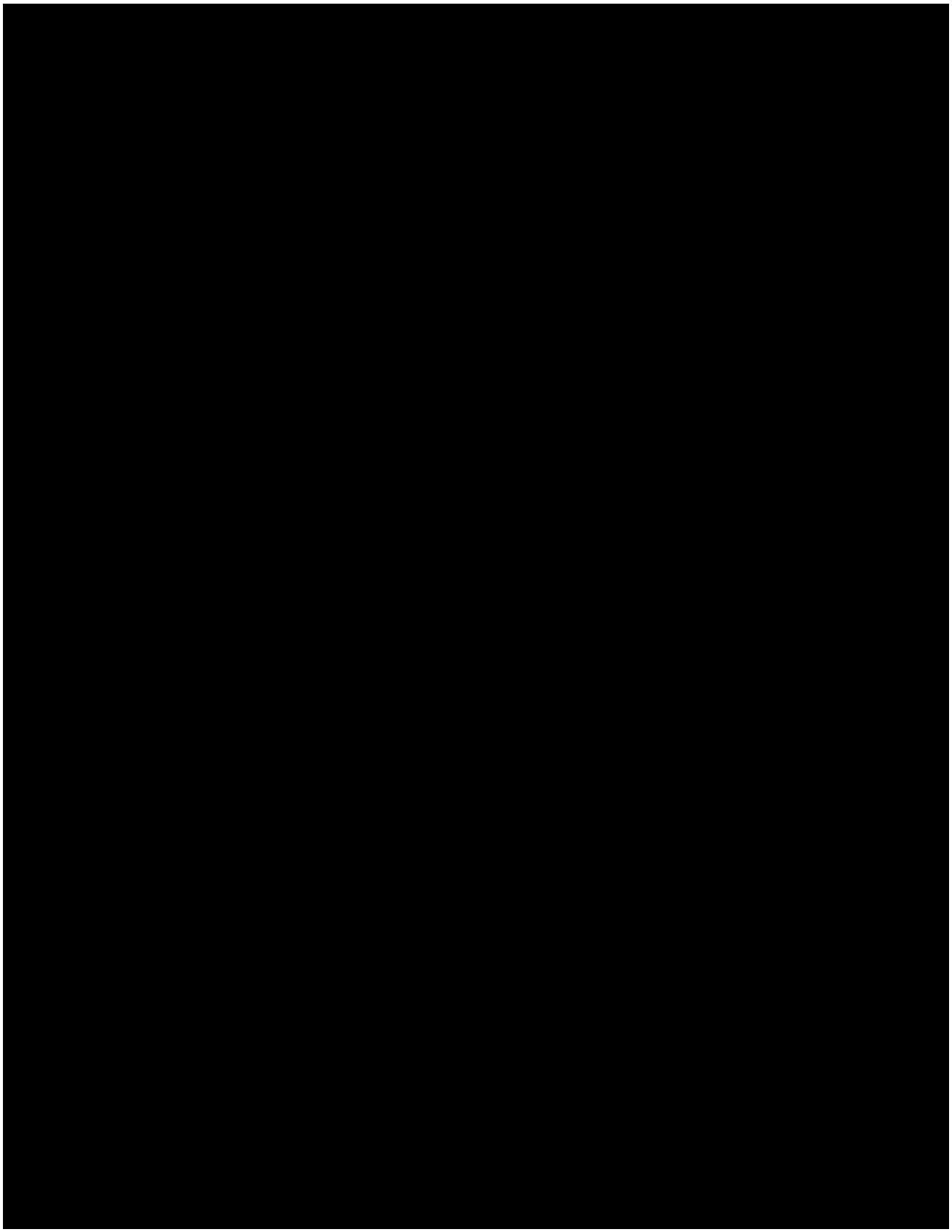

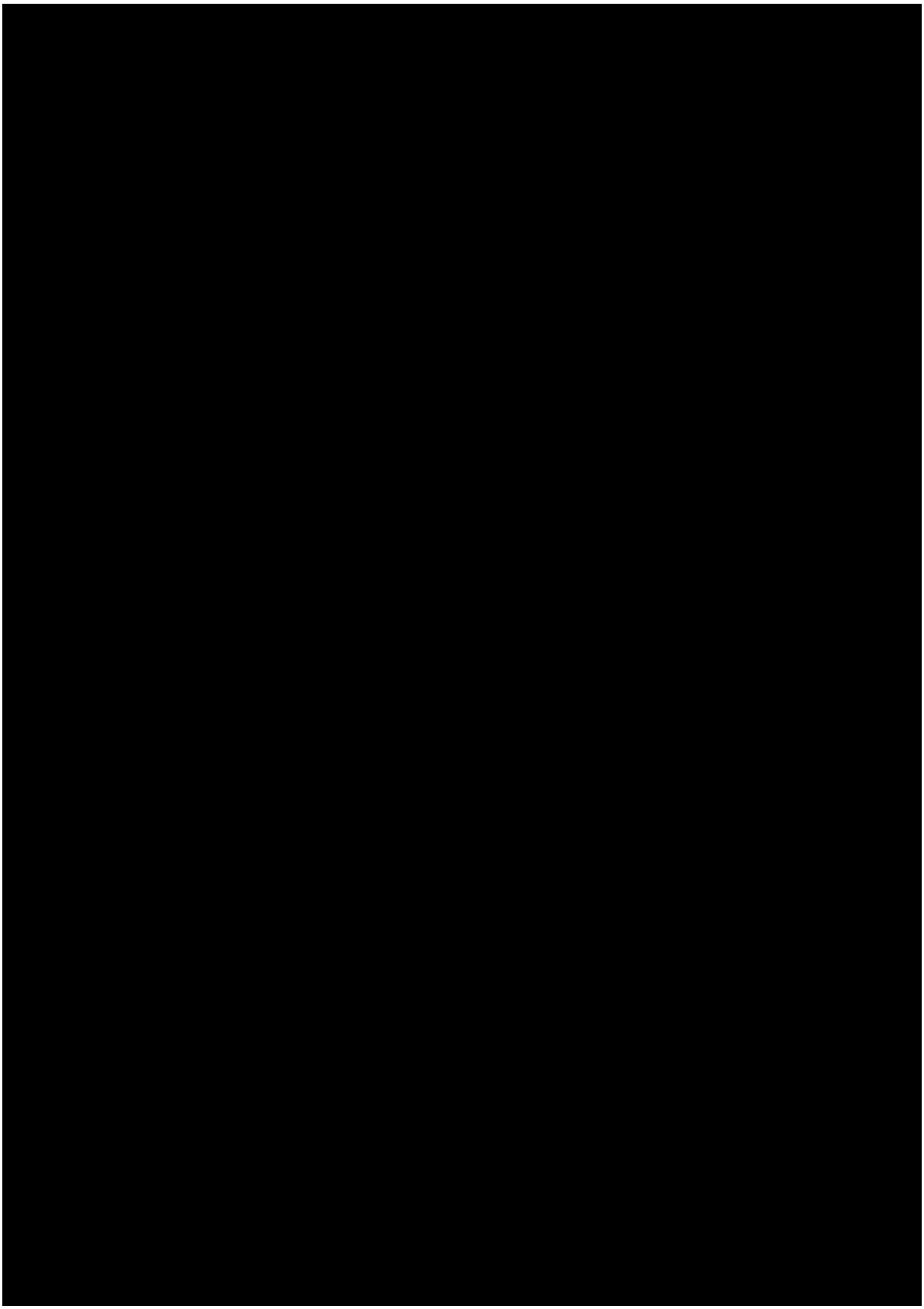

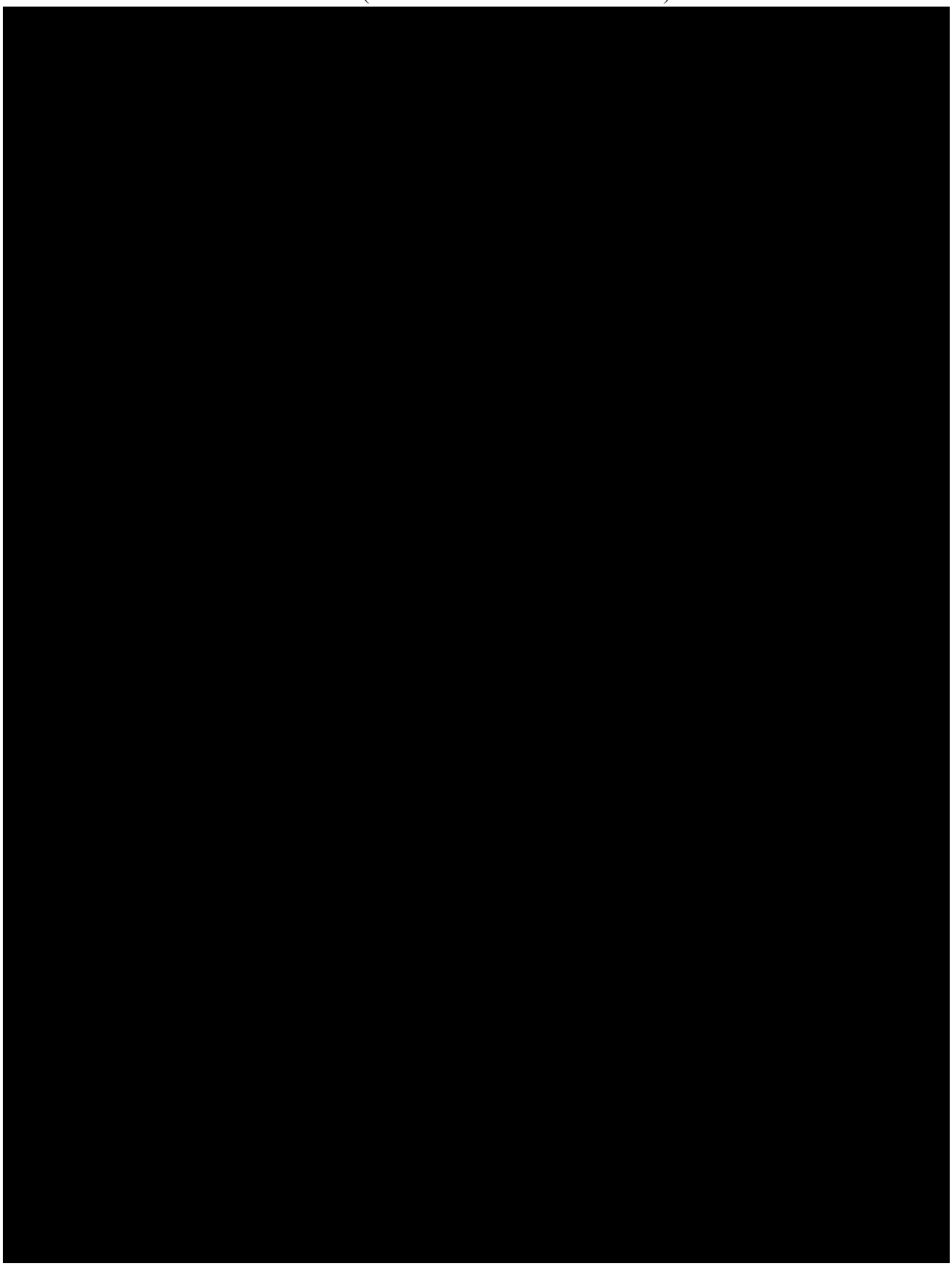

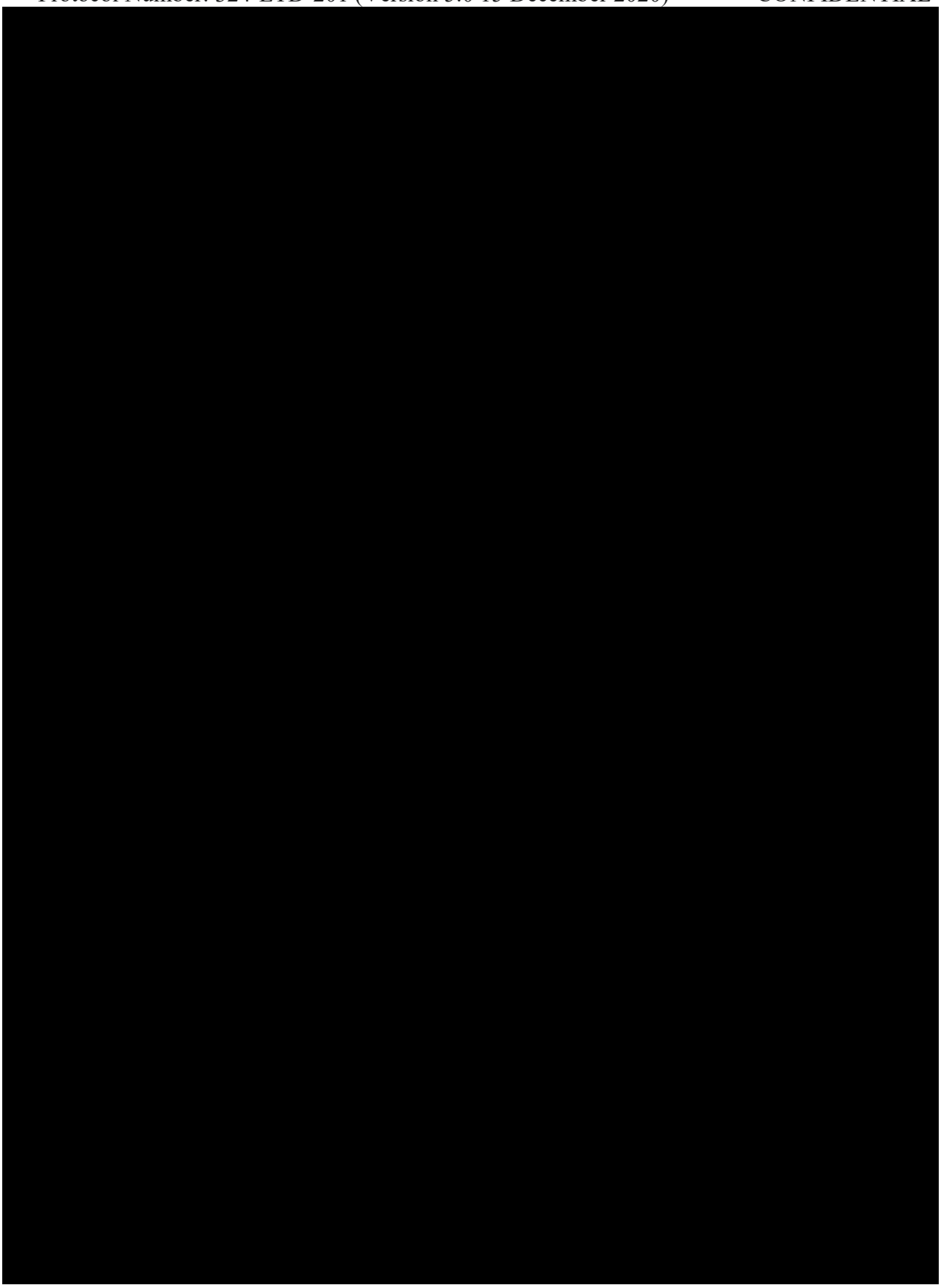

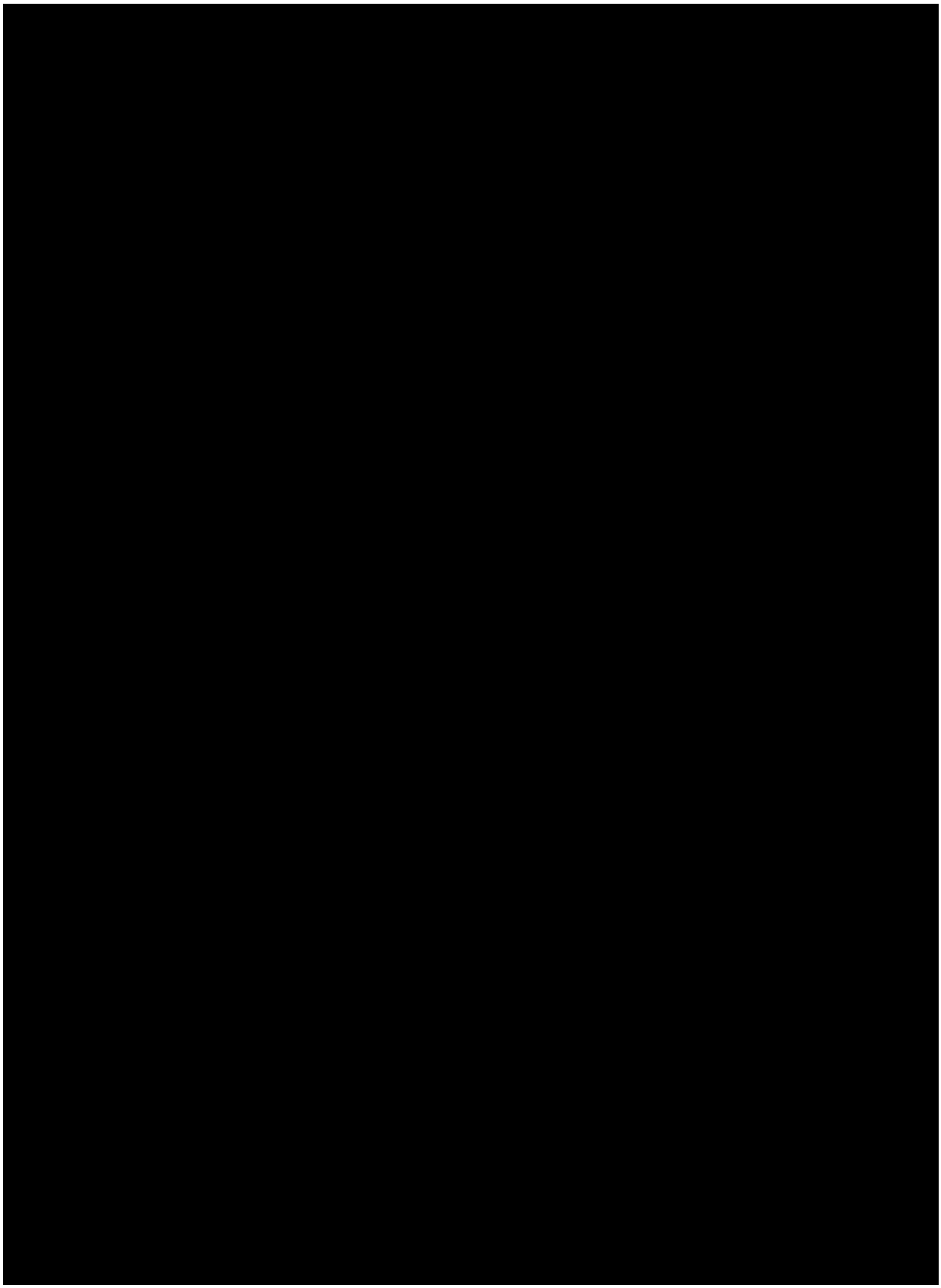

Sage_324-ETD-201_SAP_v1.0_10Mar2021_Methods

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