NCT #: NCT04625101

STATISTICAL ANALYSIS PLAN
PHASE 2

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Study Treatment: NBI-827104

Study Number: NBI-827104-CSWS2010

Study Title: Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of NBI-827104 in Pediatric Subjects with Epileptic Encephalopathy with Continuous Spike-and-Wave During Sleep

Study Sponsor: Neurocrine Biosciences, Inc.

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

CONFIDENTIAL

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
[redacted]	[redacted]
[redacted]	[redacted]
BLQ	Below the lower limit of quantification
[redacted]	
CaGI-C	Caregiver Global Impression of Change
[redacted]	[redacted]
[redacted]	[redacted]
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CI	Confidence interval
[redacted]	[redacted]
[redacted]	[redacted]
CMH	Cochran-Mantel-Haenszel
CSWS	Continuous spike-and-wave during sleep
COVID-19	Coronavirus disease 2019
[redacted]	[redacted]
C-SSRS	Suicidality measured by Columbia-Suicide Severity Rating Scale
[redacted]	[redacted]
CV	Coefficient of variation
DA	Disorders of arousal
DCP	Diagnosis Confirmation Panel
[redacted]	[redacted]
DMC	Data Monitoring Committee

Abbreviation	Term
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic case report form
EECSWS	Epileptic encephalopathy with continuous spike-and-wave during sleep
EEG	Electroencephalogram
EMA	European Medicines Agency
[redacted]	[redacted]
[redacted]	[redacted]
ET	Early termination
FDA	US Food and Drug Administration
[redacted]	[redacted]
[redacted]	[redacted]
FT4	Free thyroxine
GEC	Global executive composite
GGT	Gamma-glutamyl transferase
GMR	Geometric mean ratio
IPD	Important protocol deviations
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
NBI	Neurocrine Biosciences, Inc.
NREM	nonrapid eye movement
OLE	Open-label extension
PK	Pharmacokinetics
PT	Preferred Term
REM	Rapid eye movement
SAE	Serious adverse event
[redacted]	[redacted]
SAP	Statistical analysis plan
SAS	Statistical analysis system
SD	Standard deviation
[redacted]	[redacted]
SE	Standard error

Abbreviation	Term
SEM	Standard error of the mean
[redacted]	[redacted]
SI	International System of Units
SMQ	Standardised MedDRA Query
SOC	System organ class
SWI	Spike-wave index
[redacted]	
T3	Triiodothyronine
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
[redacted]	[redacted]
WHO	World Health Organization
[redacted]	[redacted]

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays that will be prepared to summarize the data from Neurocrine Biosciences, Inc. (NBI) Protocol NBI-827104-CSWS2010.

This SAP was developed in accordance with International Council for Harmonization E9 guidance. All decisions regarding the final analysis will be made prior to database lock and treatment unblinding and documented in this SAP. Changes to the planned analyses described in this SAP will be statistically justified and described in the clinical study report. Further information related to study design and methodology can be found in the study protocol.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
To assess the effect of NBI-827104 on the overnight epileptiform video-electroencephalogram (video-EEG) activity in pediatric subjects with EECSWS	- (Primary) Ratio of the spike-wave index (SWI) at the end of [redacted] to baseline during the first hour (60 minutes) of nonrapid eye movement (NREM) sleep based on centralized video-electroencephalogram (EEG) reading, where baseline is defined as the last value measured prior to intake of study treatment on Day 1.

[redacted]	- (Secondary)
	  - Ratio of SWI at the end of [redacted] to baseline during the first hour (60 minutes) of NREM sleep, based on centralized evaluation.
	  - Caregiver Global Impression of Change (CaGI-C) and Clinician Global Impression of Change (CGI-C) scores at the end of [redacted]
	  - Change from baseline to the end of [redacted] in Clinical Global Impression of Severity (CGI-S) scores.

[redacted]	- (Exploratory) [redacted]

Objectives	Endpoints
	• (Exploratory - continued) [redacted]
To evaluate the safety and tolerability of multiple doses of NBI-827104 in pediatric subjects with EECSWS	- Incidence of: o Adverse Events (AEs) o Suicidality measured by Columbia-Suicide Severity Rating Scale (C-SSRS) - Observed values and changes from baseline values in: o Clinical laboratory tests (haematology, chemistry) o Vital signs o 12-lead electrocardiograms (ECGs)
To assess the PK of NBI-827104 in pediatric subjects with EECSWS	• [redacted]

3. STUDY DESIGN

This is a Phase 2, multicenter, double-blind, placebo-controlled, parallel-group study designed to assess the efficacy, safety, tolerability, and PK of NBI-827104 in pediatric subjects with EECSWS. Approximately 24 male and female subjects, 4 to 12 years of age (inclusive), will be enrolled for study participation.

After providing parental or legal guardian informed consent with pediatric assent from developmentally capable pediatric subjects, subjects will be screened to determine eligibility (Days -28 to -1) before the start of study treatment dosing on Day 1. Caregiver(s) will be given a seizure diary at screening; at least 4 days of baseline seizure diary data should be obtained prior to randomization. On Day 1, eligible subjects who have a diagnosis confirmed by an external Diagnosis Confirmation Panel (DCP) will return to the study center for collection of baseline safety and efficacy assessments.

Study treatment will last for up to [redacted], and will be subdivided as follows:

- Titration period [redacted]
- Maintenance period [redacted]
- Taper period [redacted]

If an open-label extension (OLE) study is open for enrollment, eligible subjects may enter the OLE study following the completion of the [redacted] study visit at the end of the maintenance period. For subjects who enroll directly in the OLE study, the [redacted] visit will be the final study visit of the current study. For all other subjects, the end of the posttreatment safety period constitutes the end of the study.

The starting dose of study treatment is based on subjects' body weight on Day 1 as detailed in Table 2.

Table 2: [redacted]

[redacted]

[redacted]

Subjects who cannot tolerate the lowest allowable dose (ie, dose level 1) should remain in the study, but study treatment dosing will be discontinued.

[redacted]

A complete schedule of assessments is provided in Table 2 of the study protocol.

3.1. Randomization

On Day 1, eligible subjects will return to the study center for collection of baseline safety and efficacy assessments. Subjects who continue to be eligible for the study will then be randomized to NBI-827104 or placebo. The first 6 subjects (randomized 2:1; ie, 4 subjects randomized to NBI-827104 and 2 subjects randomized to placebo) will be enrolled into a sentinel cohort for the analysis and review of safety, tolerability, and PK data through [redacted] by an independent Data Monitoring Committee (DMC), before proceeding with enrollment of the remaining 18 subjects in the main cohort (randomized 2:1 [NBI-827104:placebo]).

3.2. Data Monitoring Committee and Sentinel Cohort Analysis

Ongoing review of safety and tolerability data and the unblinded analysis of sentinel cohort data (including safety, tolerability, and PK) will be conducted by the independent DMC using reports provided by an independent statistical center. The DMC has the overall responsibility of safeguarding the interests of the subjects by monitoring data obtained in the study and making appropriate recommendations based on the reported data, thus ensuring that the study is being conducted with high scientific and ethical standards.

Available PK and safety data for the sentinel cohort will be reviewed by the DMC to determine if a dose adjustment should be instituted prior to enrolling the main cohort. Dose reductions or alterations in the escalation paradigm may be recommended by the DMC to the Sponsor after the sentinel cohort analysis to achieve the targeted exposure or improve tolerability.

This study intends to target exposures equivalent to those observed with a [redacted] once-daily dose at steady state in adults (area under the concentration versus time curve during 1 dosing interval [redacted]

Efficacy analyses will not be performed as part of the sentinel cohort analysis, [redacted]

3.3. Blinding

This study includes up to [redacted] of double-blind, placebo-controlled treatment during which the subject, investigator, and all study center personnel will be blinded to the subject's treatment. The Sponsor will be blinded except for supply chain personnel who are not involved in decisions regarding subject treatment. During this treatment period, all subjects will receive NBI-827104 or placebo to be self-administered once daily.

The randomization code will be broken for an individual subject only if the subject is pregnant, experiences an SAE that the investigator feels cannot be adequately treated without knowing the subject's treatment assignment, or for regulatory reporting requirements. In the case of a medical emergency in which knowledge of the identity of the study treatment is important for subject management, the investigator has the responsibility for unblinding the randomized treatment assignment using an Interactive Web Response System. It is recommended that the investigator contact the Study Medical Monitor (or designee) before unblinding if it would not result in unnecessary delay to the immediate medical management of the subject. Documentation of the unblinding must be maintained.

Members of the DMC and individuals who generate the DMC reports will be unblinded throughout the study. Blinding will be maintained unless unblinding is necessary for subject safety.

3.4. Sample Size Considerations

The sample size is based on the primary endpoint, expressed as a ratio of SWI at the end of [redacted] to baseline. A ratio to baseline was preferred over an absolute or relative change from baseline, because of the better statistical properties of the former.

It is anticipated that at least 21 subjects will be evaluable for the primary efficacy endpoint at the end of [redacted] and at least 18 subjects will be evaluable at the end of [redacted]

Table 3:

4. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

4.1. General Statistical Procedures

All analyses described in this plan are considered a priori analyses in that they have been defined prior to locking the study database. Analyses defined subsequent to locking the database will be considered post hoc analyses and will be applied as exploratory methodology. Any post hoc analyses will be statistically justified and described in the clinical study report. Statistical analysis will be conducted, and all tables, figures, and listings generated using SAS® software (version 9.4 or later), unless stated otherwise.

Descriptive and inferential statistical methods will be used to evaluate and summarize the data from this study. The term "descriptive statistics" refers to the number of subjects (n), mean, median, SD or standard error (SE), minimum, and maximum for continuous variables. Ordinal categorical data will be summarized using median, minimum and maximum values. Number and percentage of subjects will be summarized for categorical variables. The term "inferential statistics" refers to hypothesis tests which will be performed to assess differences between the treatment group and the control group. All hypothesis tests will be tests of the null hypothesis of no difference between the groups being compared versus the two-sided alternative hypothesis that there is a difference. The level of significance (type I error) for declaring statistical significance will be 0.10 unless otherwise noted.

Summary statistics will be presented using the following decimal precision (ie, number of digits to the right of the decimal point): the minimum and maximum will have the same number of decimal places as the data; the mean, median, SD and SE will have one more decimal place than the data being summarized; the sample size (N) will be reported as an integer; percentages will be reported to one decimal place (percentages for zero counts are omitted and 100% will be reported as an integer); and p-values will be displayed using four decimal places. P-values less than 0.0001 will be displayed as < 0.0001 and p-values greater than 0.9999 displayed as > 0.9999. Confidence intervals for means will be reported to the same number of decimal places as mean values; and confidence intervals for percentages will be reported to one decimal place These rules may be modified if warranted, based on practical considerations.

All available study data will be included in relevant data displays, including data for subjects with incomplete or missing values. Replacement of missing data values with imputed values will generally not be performed unless specified otherwise in relevant endpoint subsections.

4.2. Analysis Sets

The following analysis sets are defined for this study in Table 4.

Table 4: Analysis Sets

Analysis Sets	Description
Full Analysis Set	The full analysis set includes all randomized subjects who took at least one dose of study treatment and have at least one efficacy video-EEG assessment. Subjects will be analyzed according to their randomized treatment group.
Safety Analysis Set	The safety analysis set includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment they received.
Pharmacokinetic (PK) Analysis Set	The PK analysis set comprises all subjects included in the safety analysis set who had at least one evaluable plasma concentration after initiation of NBI-827104 and did not deviate from the protocol in a way that might affect the evaluation of the PK endpoint.
Per-protocol Analysis Set	This analysis set includes all randomized subjects who completed at least 6 weeks of treatment without protocol deviations that may affect the evaluation of the primary endpoint. Subjects will be analyzed according to their randomized treatment group.

Summaries of subject disposition, analysis set inclusion/exclusion status, and important protocol deviations (IPD) will be based on all randomized subjects. Efficacy summaries and demographics/baseline characteristics are based on the full analysis set. The PK analysis set will be employed in the analysis of the plasma concentrations and PK parameters. All other summaries are based on safety analysis set unless otherwise noted.

4.3. General Definitions

4.3.1. Baseline Definition

The assessments collected at Day 1 prior to study treatment will serve as the baseline value for all assessments. If a Day 1 visit value is not available, then the last measurement collected prior to study treatment will serve as baseline.

Baseline values for seizure endpoints will be determined from the immediate 28 days prior to Day 1.

4.3.2. Derived and Transformed Data

Change from baseline is calculated as the postbaseline value minus the baseline value; a negative value will represent a decrease at the postbaseline visit. Percent change from baseline is calculated as (change from baseline/baseline value × 100). If either the baseline or postbaseline value is missing, the change from baseline and/or percent change from baseline will also be missing. The percent change from baseline will also be missing if the baseline value is equal to zero.

The values for monthly seizure frequency in a given period (i.e. Baseline, Treatment up to [redacted], Treatment up to [redacted] will be derived as follows:
28 x Total number of countable seizures during [Period]/Total number of days in [Period] with nonmissing diary data

4.3.3. Study Day

Study day is calculated relative to the date of Day 1, where Day 1 is defined as the date the subject received their first dose of study drug. If the date of interest occurs on or after Day 1, then the study day will be calculated as: date of interest – date of Day 1 + 1. If the date of interest occurs prior to Day 1, then the study day will be calculated as: date of interest – date of Day 1.

4.3.4. Early Termination Data

Early termination (ET) data collected at postbaseline unscheduled visits will be mapped to the next subsequent visit where the applicable assessment would have been performed for the purpose of statistical summarization. ET data collected at a scheduled visit per the protocol schedule of assessments will be mapped to that scheduled visit for applicable data summaries.

4.3.5. Handling of Missing Data

4.3.5.1. Start Dates for Adverse Events

Missing and incomplete dates for AEs will be imputed for the purpose of estimating the time of the event in relationship to study treatment.

The imputation rules for AE start dates are as follows:

- If the date is completely missing, the date will be imputed as the date of the first dose of study drug;
- If only the day is missing, the date will be imputed as the date of the first dose of study drug if the month and year of the AE start date match the month and year of the first dose of study drug; otherwise, the missing day will be imputed as the first day of the month;
- If both the day and month are missing, the date will be imputed as the date of the first dose of study drug if the AE start date is in the same year as the first dose of study drug; otherwise, the missing day and month will be imputed as 01 January;
- If any of the above imputations result in a start date that is later than an existing (not imputed) end date for the event, the start date will be imputed as the end date.

There will be no imputation for AE stop dates.

4.3.5.2. Start and Stop Dates for Antiseizure and Rescue Medications

Missing and incomplete dates for concomitant anti-seizure medications and rescue medications will be imputed for the purpose of estimating the time of medication usage relative to study treatment.

The imputation rules for concomitant medication start dates are as follows:

- If the date is completely missing, the date will be imputed as the date of the subject's first dose of study drug;
- If only the day is missing, the date will be imputed as the date of the first dose of study drug if the concomitant medication start date is in the same month and year as the first dose of study drug; otherwise, the missing day will be imputed as the first day of the month;
- If both the day and month are missing, the date will be imputed as the date of the first dose of study drug if the concomitant medication start date is in the same year as the first dose of study drug; otherwise, the missing day and month will be imputed as 01 January.

If any of the above imputations result in a start date which is later than an existing (not imputed) medication stop date, the start date will be imputed as the stop date.

The imputation rules for concomitant medication stop dates are as follows:

- If the date is completely missing, the date will be imputed as the date of the subject's last dose of study drug;
- If only the day is missing, the date will be imputed as the date of the last dose of study drug if the concomitant medication stop date is in the same month and year as the last dose of study drug; otherwise, the missing day will be imputed as the last day of the month;
- If both the day and month are missing, the date will be imputed as the date of the last dose of study drug if the concomitant medication stop date is in the same year as the last dose of study drug; otherwise, the missing day and month will be imputed as 31 December.

If any of the above imputations result in a stop date which is earlier than an existing (not imputed) medication start date, the stop date will be imputed as the start date.

Missing and partial dates will not be imputed for other concomitant medications.

4.4. Coding Dictionaries

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 24.0). Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (March 2020 B3 Global version).

5. STUDY POPULATION

5.1. Disposition

The summary of subject enrollment and disposition will include:

- The total number of subjects who provided informed consent and were screened
- The following categories will be presented by treatment group and overall. The number of subjects randomized will serve as the denominator to calculate percentages.
  - Randomized but not treated
  - Received study drug
  - Completed study drug dosing
  - Completed titration period
  - Completed maintenance period
  - Discontinued study drug dosing, including reasons
  - Completed study
  - Discontinued study, including reasons

5.2. Summary of Analysis Sets

A summary of the number and percentage of subjects included in (and excluded from, as applicable) each analysis set will be provided for each treatment group.

5.3. Protocol Deviations

Protocol deviations will be reviewed and tracked as described in the study-specific Protocol Deviation Plan. Prior to database lock, all major protocol deviations that have been entered into the clinical trial management system will be exported to a file and integrated into the study data.

The study team will review a listing of all major protocol deviations and determine which deviations are important protocol deviations (IPDs). IPD are protocol deviations that might significantly affect the completeness, accuracy and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. The assessment of IPDs will be performed prior to database lock and unblinding of the randomized treatment assignments.

A summary of the number and percentage of all randomized subjects with IPD by deviation category will be presented by treatment group and overall. The summary will be repeated for the subset of IPD that are related to the coronavirus disease 2019 (COVID-19) pandemic.

All major protocol deviations will be presented in a data listing and any that are classified as IPD will be flagged in the listing. Any major protocol deviations related to the COVID-19 pandemic will also be flagged in the listing.

5.4. Demographic and Baseline Characteristics

Demographics and study baseline (ie, last measurement collected prior to the first dose of study drug) characteristics will be summarized descriptively by treatment group and overall for the full analysis set. The following variables will be summarized:

- Demographics: age, sex, ethnicity, race, country
- Baseline subject characteristics: height [cm], weight [kg], body mass index [BMI, kg/m^2]
- Baseline severity of illness: CGI-S
- Baseline seizures (yes/no)
- Baseline SWI during first hour of NREM sleep
- Medications: number of current antiseizure medications, number of prior antiseizure medications, rescue medications [yes/no], non-drug antiseizure treatments [yes/no]
- Seizure and CSWS history: age at CSWS diagnosis, duration since CSWS diagnosis, age at symptom onset for CSWS, etiologic subgroup (structural, genetic, unknown), seizure history [any, tonic-clonic, tonic, atonic, focal onset seizures (FOS) with an identifiable motor component, other], age at seizure onset, family history of seizure activity

6. IMPACT OF COVID-19 PANDEMIC

This section describes analyses and summaries that will be produced to help determine the potential impact of the COVID-19 pandemic on the study conduct/data and additional details regarding how data that is potentially impacted by the COVID-19 pandemic will be handled in the analysis plan. It is in alignment with the guidance put forth by the US Food and Drug Administration (FDA; Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency [March 2020, updated January 2021]) and European Medicines Agency (EMA; Points to consider on implications of Coronavirus disease [COVID-19] on methodological aspects of ongoing clinical trials [March 2020]).

To help understand the impact of the COVID-19 pandemic on the clinical trial data, the following listings will be generated:

- A listing of all subjects affected by the COVID-19 pandemic. The listing will identify subjects who experience at least one of the following situations due to the COVID-19 pandemic (additional situations may be included):
    - Discontinued study due to COVID-19
    - Presumed or confirmed diagnosis of COVID-19
    - Had at least one COVID-19 pandemic-related major protocol deviation
    - Missed at least one study visit or assessment due to COVID-19
    - Required at least one assessment to be collected using a method other than what is defined in the protocol (eg, remotely) due to COVID-19
- A listing of subjects who withdrew from study due to the COVID-19 pandemic, which will include the specific reasons.
- A listing by subject of visits and assessments affected by the COVID-19 pandemic (eg, missing, partial, collected remotely).

The above listings may be omitted if it is known there was no impact of the COVID-19 pandemic on the study conduct.

The broad Standardised MedDRA Query (SMQ) of COVID-19 will be utilized to identify preferred terms (PTs) pertaining to subjects with a presumed or confirmed diagnosis of COVID 19 (using MedDRA version 24.0).

[redacted]

7. EFFICACY

The efficacy endpoints and planned analysis methods are described below. Unless otherwise noted, the full analysis set will be used for all efficacy analyses, and descriptive statistics for observed values and changes from baseline will be presented by treatment group (NBI-827104 versus placebo) and nominal visit according to the protocol schedule of assessments.

7.1. Multiple Comparisons and Multiplicity

There will be no adjustments for multiple comparisons.

7.2. Statistical Models

7.2.1. Continuous endpoints

The continuous efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model, which includes the change from baseline to the respective postbaseline visit where the endpoint is being evaluated. The model will include the relevant baseline value as a covariate, and treatment group (NBI-827104; placebo). The treatment group difference at the postbaseline visit and the 90% CIs will be obtained from the ANCOVA model.

For endpoint data departing from the normal distribution, values will be log-transformed prior to analysis including the baseline covariate. The estimates of the mean differences between treatment groups will be exponentiated to original units and reported as geometric mean ratios (as a percent). The 2-sided 90% CIs associated with each difference will be calculated and exponentiated back to original units (displayed as percentages) for reporting purposes.

An example of the SAS software code is provided below. [redacted]

7.2.2. Categorical endpoints

Ordinal categorical efficacy endpoints will be analyzed using the Jonckheere-Terpstra test to compare treatment groups (NBI-8027104 versus placebo). Binary efficacy endpoints will be analyzed using Fisher's exact test. An example of the SAS software code is provided below.

[redacted]

[redacted]

7.3. Interim Analysis

No interim analysis for efficacy is planned for this study.

7.4. Primary Efficacy Endpoint

The primary efficacy endpoint is the log-transformed ratio of SWI at the end of [redacted] to baseline during the first hour (60 minutes) of NREM sleep based on centralized video-EEG reading, where baseline is defined as the last value measured prior to intake of study treatment on Day 1.

Inpatient overnight video-EEG using a standard international 10/20 EEG recording setup and concurrent video will be conducted [redacted] The overnight video-EEG recording will be centrally read and used to compute the endpoints [redacted] As an outcome measure of this study to quantify electrographic CSWS activity, the SWI is defined as the percentage of seconds with ≥1 spike-wave complex(es) during defined periods of overnight NREM sleep.

Descriptive statistics will be presented for SWI during the first hour of NREM sleep by treatment group and visit for the observed and change from baseline values.

The primary estimand is defined by the following:

Population: All randomized subjects with CSWS defined by study inclusion/exclusion criteria who have taken at least one dose of study drug and have at least one post-baseline efficacy video-EEG assessment.

Variable (or endpoint) to be obtained for each subject: Log-transformed ratio of SWI at [redacted] to SWI at baseline

Population-level summary: Ratio of geometric mean ratio (GMR) of SWI at [redacted] to baseline in the NBI-827104 group divided by the GMR of SWI at [redacted] to baseline in the placebo group

The least-squares mean treatment difference for this endpoint will be estimated using an ANCOVA model with treatment group as a fixed factor and baseline SWI (log-transformed) as a

covariate. The treatment group difference at [redacted] and the 90% CI will be obtained from the ANCOVA model.

The associated summary statistic on a treatment group level is the geometric mean ratio (GMR) of SWI at [redacted] to baseline (obtained by exponentiating the mean of the log-transformed ratios). A GMR <1 indicates an improvement from baseline in the treatment group.

Handling of intercurrent events: Treatment-policy approach whereby data is used whether or not an intercurrent event occurs akin to intent-to-treat principle.

[redacted]

7.5. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Ratio of SWI at the end of [redacted] to baseline during the first hour (60 minutes) of NREM sleep, based on centralized evaluation
- CaGI-C score at [redacted]

- CaGI-C score at [redacted]
- CGI-C score at [redacted]
- CGI-C score at [redacted]
- Change from baseline to [redacted] in CGI-S score
- Change from baseline to [redacted] in CGI-S score

7.5.1. SWI during the first hour at [redacted]

The ratio of SWI at the end of [redacted] to baseline during the first hour (60 minutes) of NREM sleep, based on centralized evaluation, will be summarized descriptively by treatment group and visit, and change from baseline analyzed with ANCOVA models similar to those used for the primary endpoint.

7.5.2. CaGI-C Scores at [redacted]

The CaGI-C is a 7-point scale and provides a global evaluation of the subject's change in CSWS symptoms since baseline from the caregiver's perspective. If possible, the same person should rate the CaGI-C at all visits (ie, [redacted] [or ET]). Subjects can be scored from 1-7: Very much improved (1), Much improved (2), Minimally improved (3), No change (4), Minimally worse (5), Much worse (6), Very much worse (7).

The number and percentage of subjects by CaGI-C categories will be summarized by treatment group and postbaseline visit. In addition, subjects whose CaGI-C score is either a 1 ("Very much improved") or a 2 ("Much improved") will be classified as responders. CaGI-C ordinal categories, as well as binary response status, will be analyzed at [redacted] using the methods described in Section 7.2.2 for categorical efficacy endpoints.

7.5.3. CGI-C at [redacted]

The CGI-C, which is based on a 7-point scale (range: 1=Very Much Improved to 7=Very Much Worse) requires the clinician to rate the overall change in the subject's CSWS symptoms since the subject started taking the study drug, relative to baseline.

The number and percentage of subjects by CGI-C categories will be summarized by treatment group and postbaseline visit. In addition, subjects whose CGI-C score is either a 1 ("Very much improved") or a 2 ("Much improved") will be classified as responders. CGI-C ordinal categories, as well as binary response status, will be analyzed at [redacted] using the methods described in Section 7.2.2 for categorical efficacy endpoints.

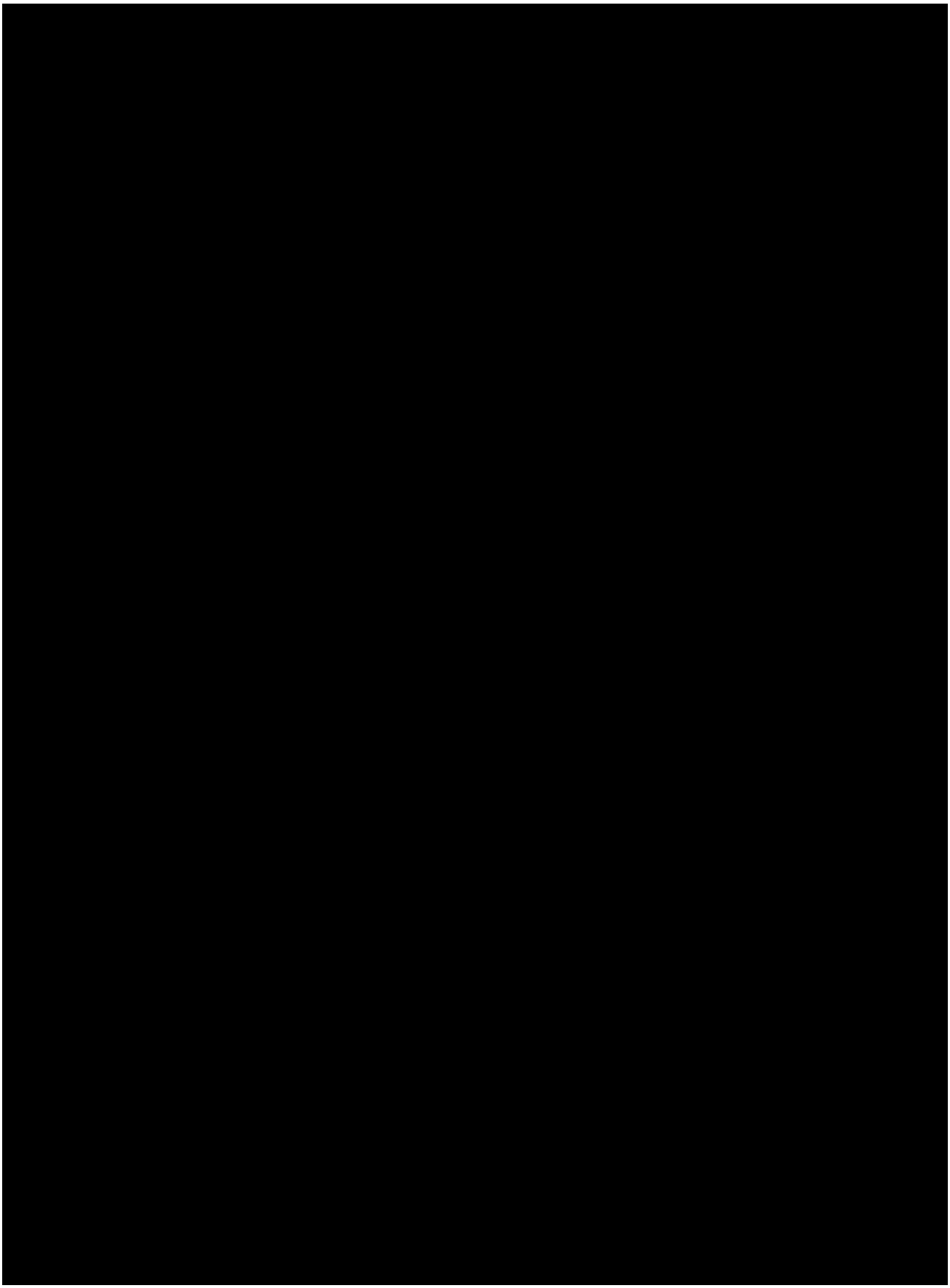
7.5.4. CGI-S at [redacted]

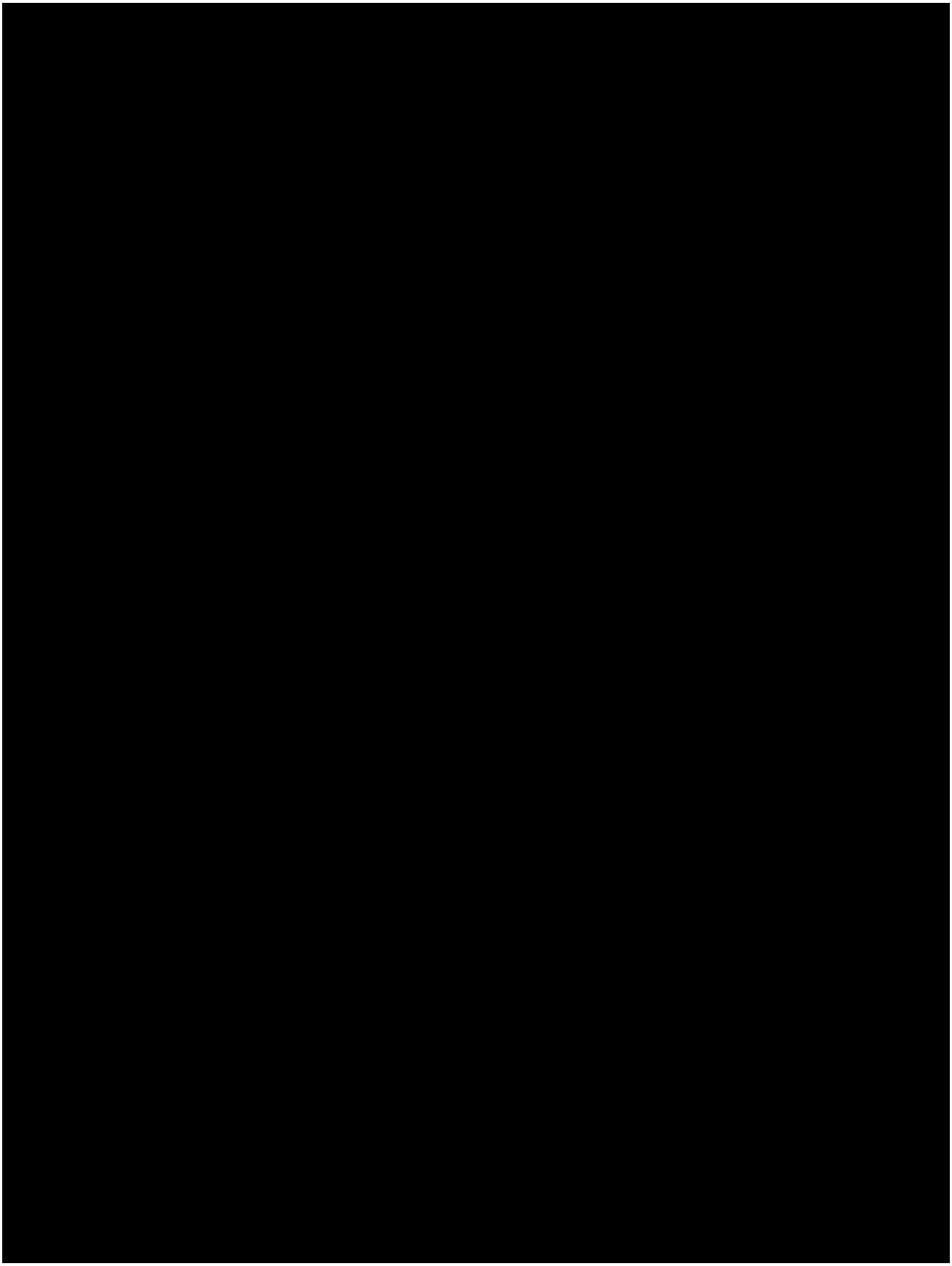
The CGI-S is a 7-point scale that required the clinician to rate the severity of the subject's illness at the time of assessment (ie, Day 1, and [redacted] [or ET]), relative to the clinician's past experience with patients who have CSWS. Subjects can be scored from 1-7: Normal, not at all ill (1), Borderline ill (2), Mildly ill (3), Moderately ill (4), Markedly ill (5), Severely ill (6), Among the most extremely ill patients (7).

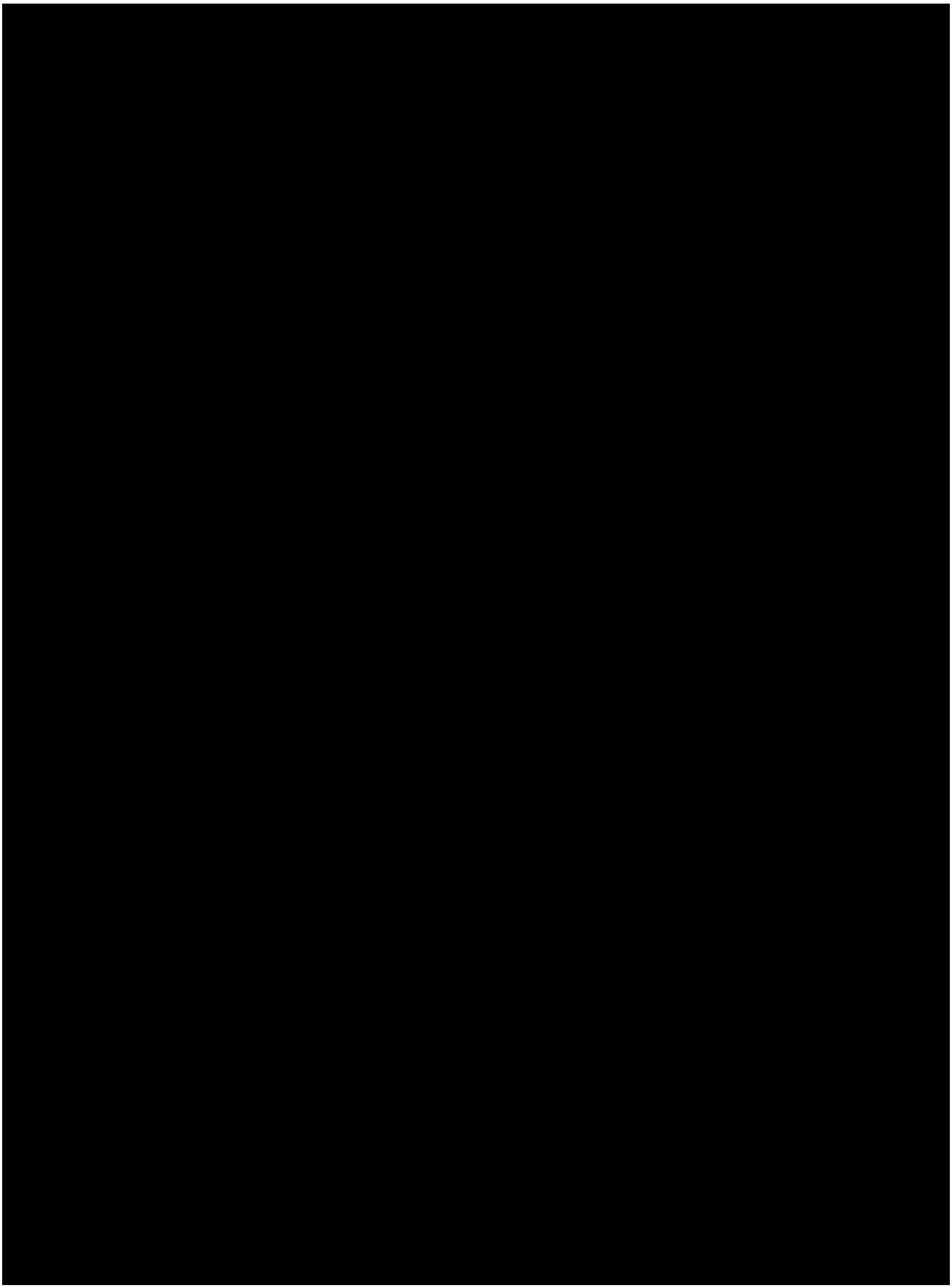
Number and percentage of subjects by CGI-S categories will be summarized by treatment group and visit. In addition, subjects with at least a 1-point improvement from baseline in CGI-S will be classified as responders. CGI-S ordinal categories, as well as binary response status, will be analyzed at [redacted] using the methods described in Section 7.2.2 for categorical efficacy endpoints. Shift tables for CGI-S categories from baseline to [redacted] will be presented.

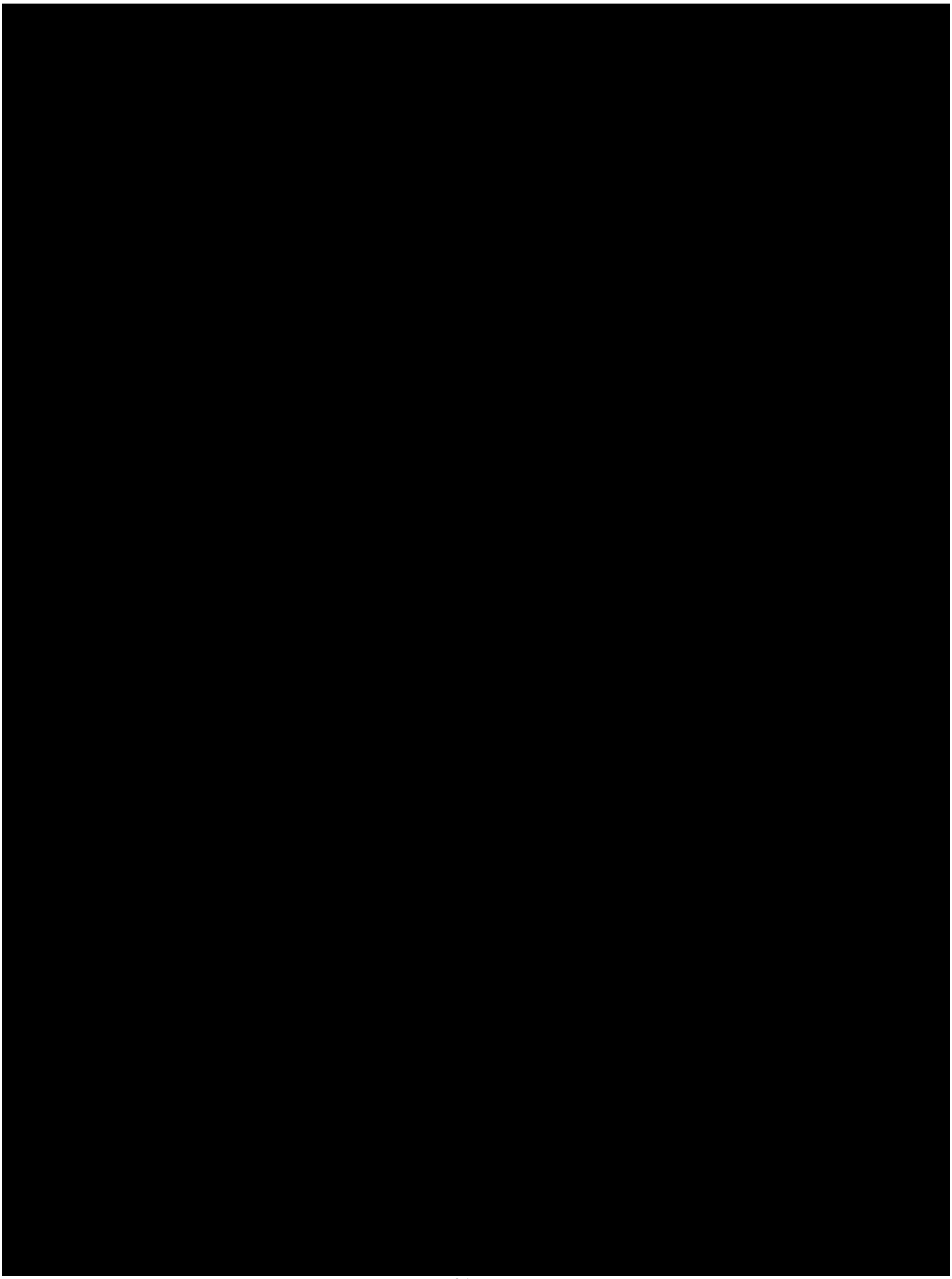
7.6. Exploratory Efficacy Endpoints

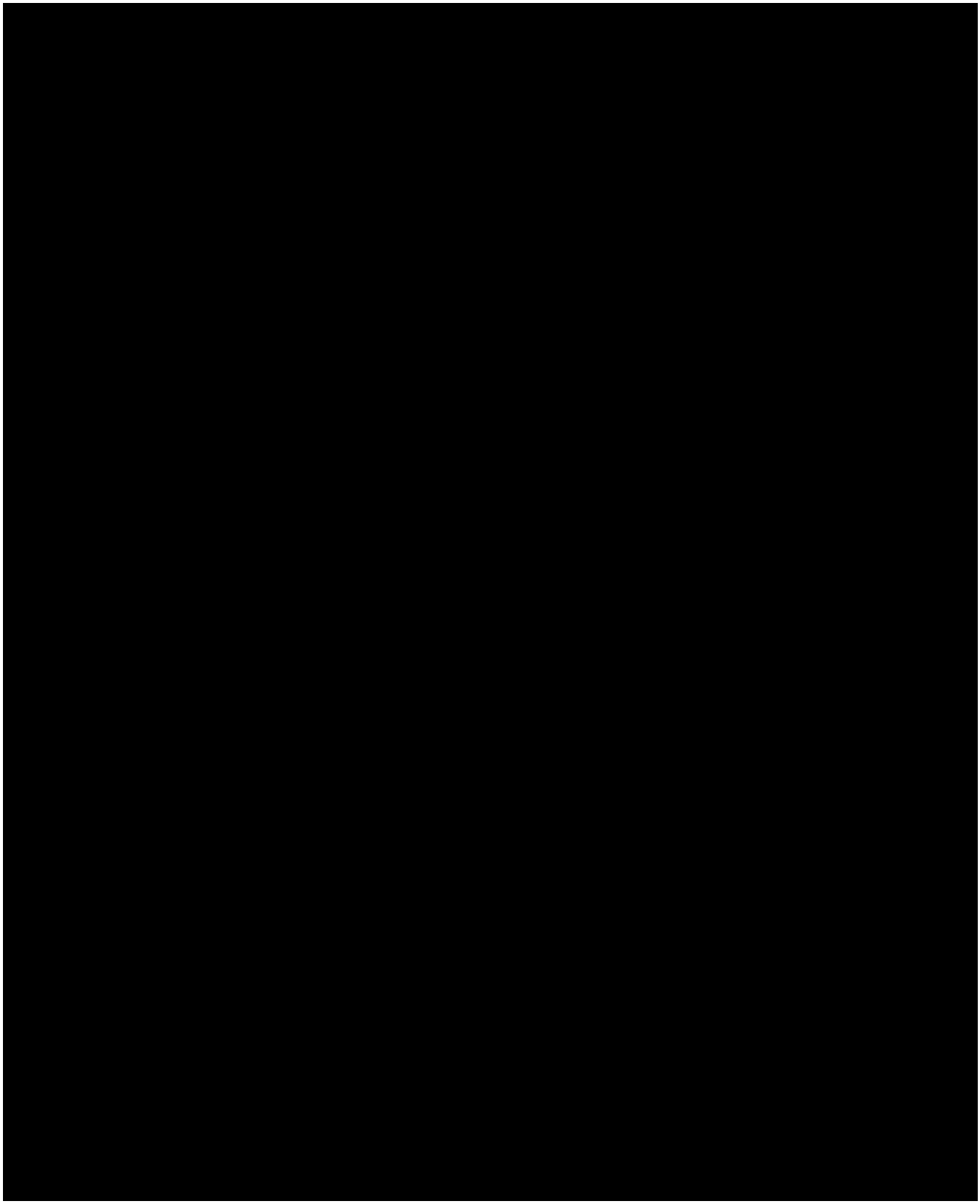
[redacted]

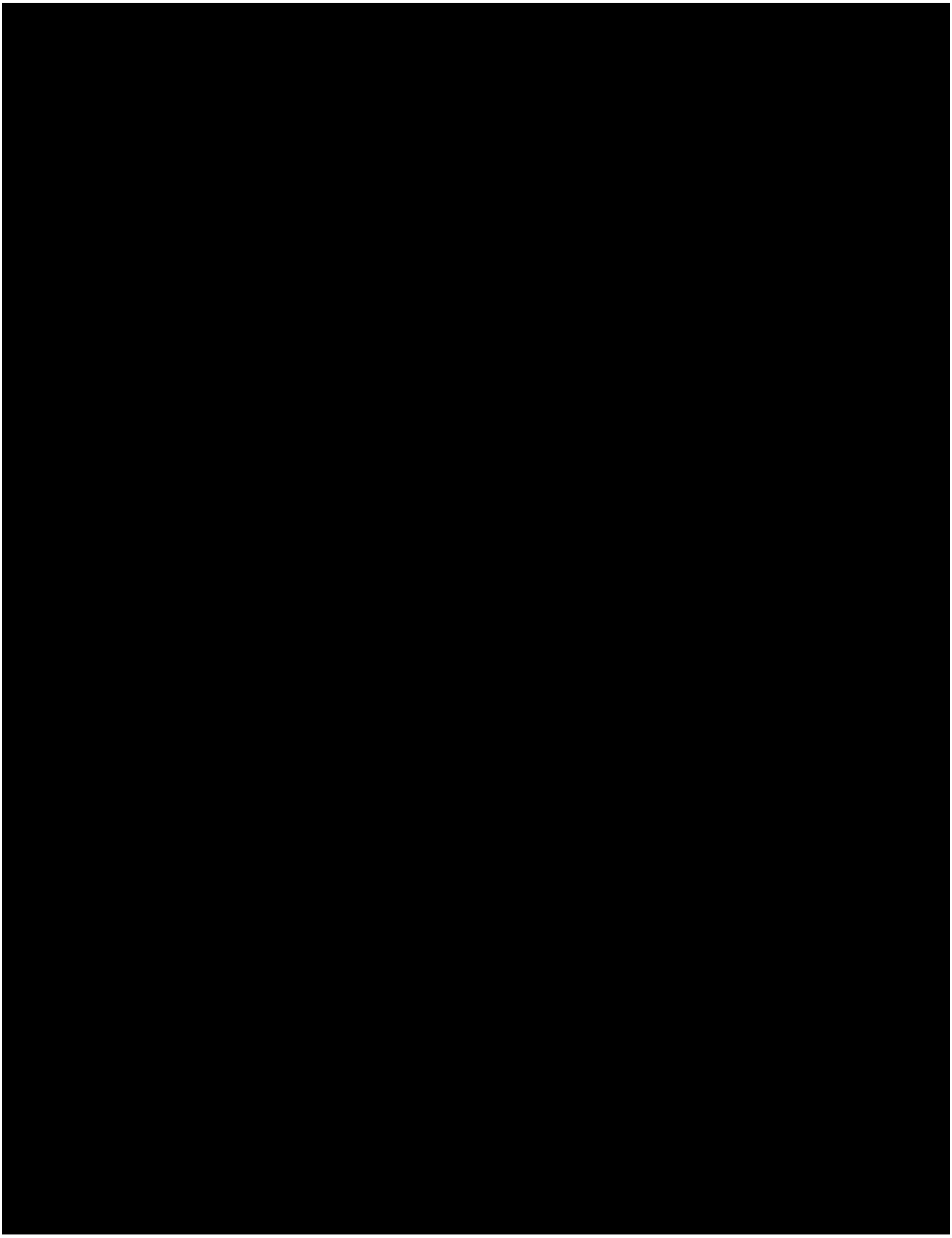


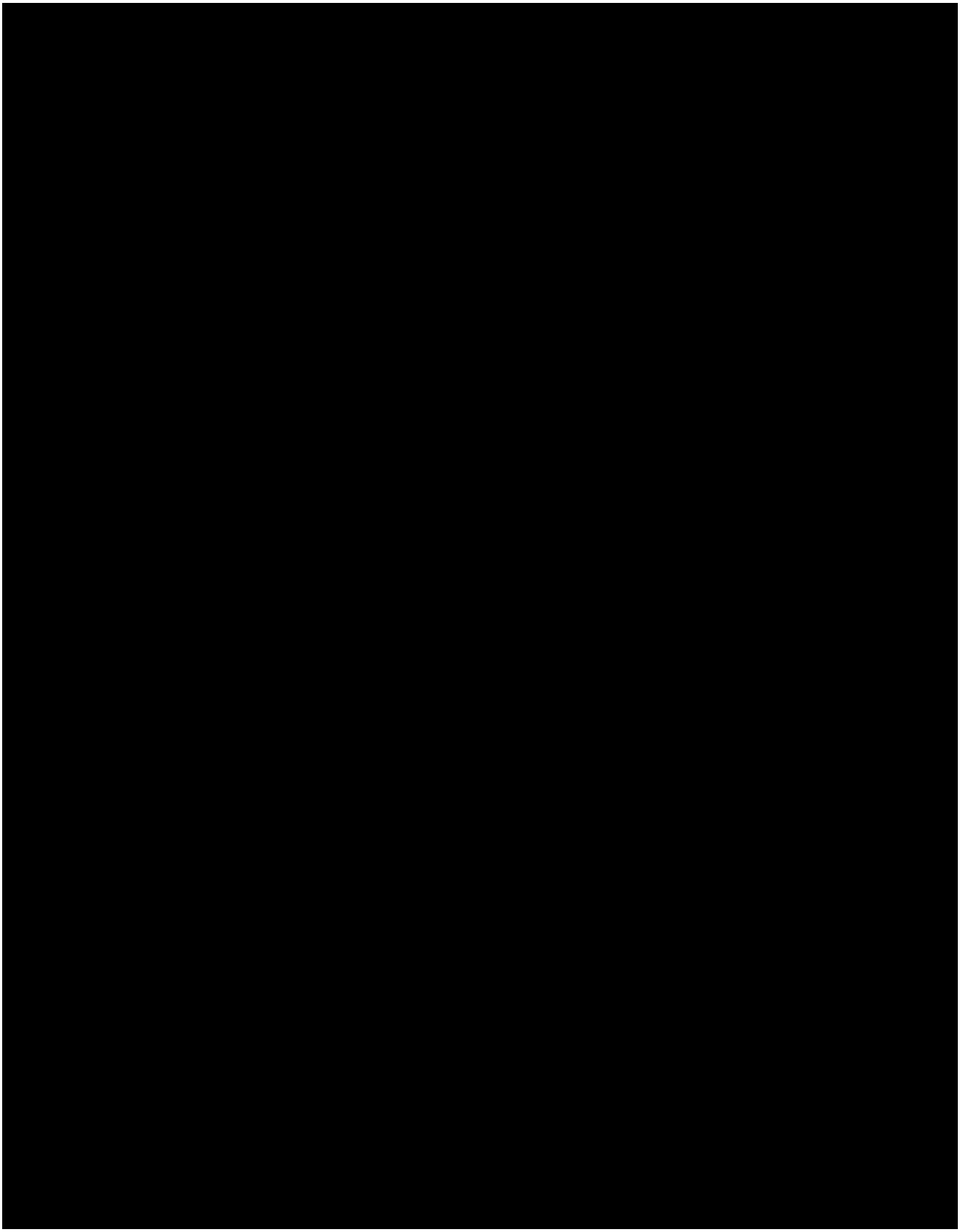


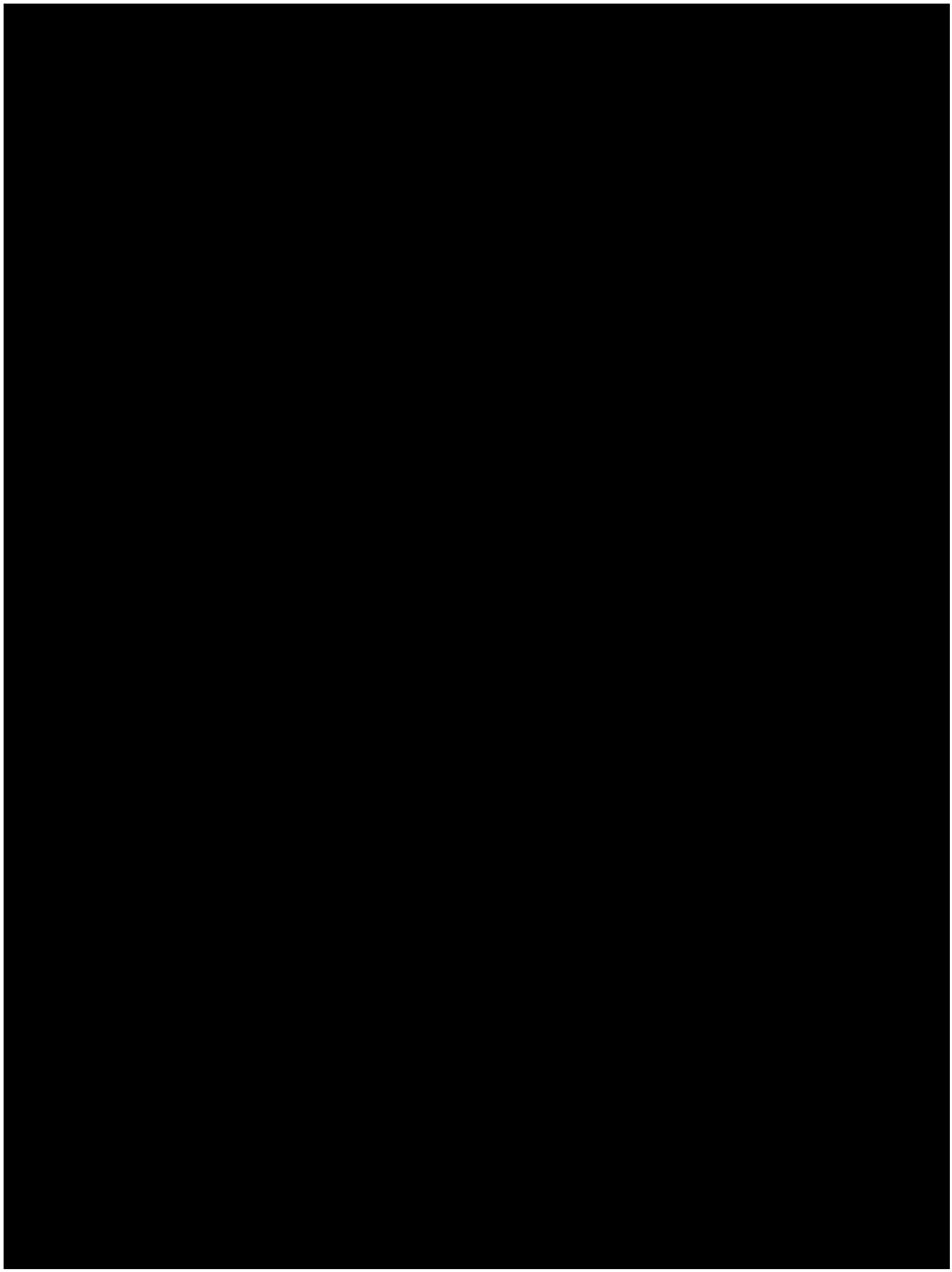












8. PHARMACOKINETIC ANALYSIS

8.1. Plasma Concentrations

Plasma concentrations of NBI-827104 will be summarized per nominal timepoint overall and by body weight group using the PK analysis set. The number and percentage of subjects with data and the number and percentage of subjects with values below the lower limit of quantification (BLQ) and quantifiable results will be given.

[redacted]

All BLQ values will be set equal to zero in the plasma concentration summaries.

8.2. [redacted]

[redacted]

[redacted]

Table 5: [redacted]

9. SAFETY

The safety objective of the study is to characterize the safety profile of NBI-827104 as measured by TEAEs and SAEs, clinical laboratory tests, vital signs, ECG, and the C-SSRS. All outputs for safety endpoints will be based on the safety analysis set. The analysis of the safety data will be based on descriptive statistics and presented by treatment group according to the study visit unless otherwise noted. Data from the neurological and ophthalmic examinations will not be summarized because any abnormal results were assessed for AE reporting by the investigator and will be captured in the AE summaries. Safety data will not be subject to any imputation and will be summarized on an observed case basis. No formal hypothesis-testing analysis of safety data will be performed.

9.1. Study Drug Dosing and Compliance

The duration of exposure to study drug will be calculated as: last dose date – first dose date +1. Duration of exposure will be summarized with descriptive statistics by treatment group.

Dose adjustments will be summarized for each postbaseline visit. The number and percentage of subjects whose dose is escalated, maintained, or reduced will be presented by treatment group. Dose reductions at unscheduled visits will be included in the summary for the next scheduled visit. Subjects who prematurely discontinue study at a visit will not be included in the visit summary unless they had a dose reduction at an unscheduled visit after the previous scheduled visit. The table will include the total number and percentage of subjects with a dose reduction at any time during the treatment period through the end of maintenance. Note that changes in dosage will be presented for the control group, even though no actual changes in study drug are occurring.

A summary of dose levels in subjects in the NBI-827104 treatment group will be presented for each postbaseline visit. Descriptive statistics of the last dose assigned prior to the visit (including at unscheduled visits) will be presented. The number and percentage of subjects receiving each dose will also be presented for each postbaseline visit.

The site will enter into the eCRF whether the subject's dosing compliance since the previous visit was within 80% and 120% inclusive. The number and percentage of subjects in each treatment group who are dosing compliant, <80%, and >120% will be presented for each postbaseline visit.

9.2. Adverse Events

A treatment-emergent adverse event (TEAE) is an AE not present prior to the initiation of study drug dosing, or is an already present event that worsens either in intensity or frequency following the initiation of study drug dosing. Investigators will be asked to respond "Yes" or "No" on the eCRF as to whether the AE started after the subject took the first dose of study drug. An AE with a response of "Yes" will be classified as a TEAE. If the investigator's response is missing, then the treatment emergent status will be derived based on the AE onset date and time relative to the date and time of the subject's first dose of study drug. If the AE onset date and time are unknown, it will be assumed that the AE is a TEAE. If the AE onset time is unknown but the AE onset date is the same date as the first dose of study drug, it will be assumed that the AE is a TEAE. Adverse events with an onset date after the last dose date and on or before the last dose

date plus 14 days will be considered post-treatment emergent and will be tabulated by treatment groups. See details for imputing missing/partial start dates (Section 4.3.5.1). There will be no imputation for AE stop dates.

TEAEs, categorized by MedDRA system organ class (SOC) and/or PT, will be summarized in frequency tables. The frequency tables will include the number and percentage of unique subjects experiencing each event one or more times by treatment group.

An overall summary table will be provided which summarizes the number and percentage of unique subjects with any TEAE, treatment-emergent SAE, TEAE leading to study drug dose reduction, TEAE leading to study drug discontinuation, TEAE leading to study discontinuation, and TEAE resulting in death. The summary table will also include the frequency distribution of the maximum TEAE intensity (mild, moderate, severe) reported for each subject.

The following summary tabulations will also be presented by treatment group. Unless otherwise noted, the tables will be sorted in alphabetical order. The first line of the table will display the number and percentage of subjects with at least one of the following adverse event categories:

- TEAEs, classified by SOC and PT
- Any TEAEs, classified by PT, displayed in a descending order by frequency in the NBI-827104 treatment group
- Treatment-emergent SAEs by SOC and PT
- TEAEs leading to study drug dose reduction by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT
- TEAEs leading to death by SOC and PT
- Post-treatment emergent AEs by SOC and PT

A listing of TEAEs resulting in study drug discontinuation will be provided which includes subject ID, treatment group, last treatment received prior to the onset time of the TEAEs leading to study drug discontinuation, study day of the discontinuation, and other relevant information from the AE eCRF. Note that “last treatment received prior to the onset time of the TEAEs leading to study drug discontinuation” reflects the actual dose received prior to the AE.

Separate listings of TEAEs resulting in study drug dose reductions, SAEs, and fatal AEs will also be provided. In the event that no subjects experience study drug dose reductions, SAEs, or fatal AEs, the blank listing shell will be presented with text printed in the center of the listing such as “No serious adverse events occurred during this study.”

9.3. Clinical Laboratory Data

The hematology and clinical chemistry data will be summarized with descriptive statistics by treatment group and visit. Both observed values and changes from baseline will be summarized.

Shift tables will be presented for selected clinical laboratory variables based on the reference range-based categories of “Low,” “Normal,” or “High.” A clinical laboratory variable value will

be assigned to one of these three categories according to the reference ranges provided by the central clinical laboratory.

Two shift tables will be presented within the double-blind treatment period: shifts from baseline to the end of the titration and maintenance periods. Each shift table will have three rows and three columns, with rows reflecting the reference range category at baseline, and columns reflecting the reference range category at the specified postbaseline visit. A “Total” row and “Total” column will also be included. Subjects with a missing baseline value or who do not have postbaseline data will not be included in the tables for that variable. The number and percentage of subjects in each shift category will be displayed in the table; percentages will be based on the number of subjects included in the table.

Shift tables will be presented for the following clinical laboratory variables:

- aspartate aminotransferase (AST),
- alanine aminotransferase (ALT),
- gamma-glutamyl transferase (GGT),
- total bilirubin,
- creatine kinase,
- creatinine,
- blood urea nitrogen,
- white blood cell count,
- hemoglobin,
- platelet count,
- Free triiodothyronine (T3),
- Free thyroxine (FT4) and
- Thyroid stimulating hormone (TSH).

9.4. Vital Signs

The vital signs data, including weight, BMI, orthostatic blood pressures and heart rate (calculated as standing value minus sitting value), will be summarized with descriptive statistics by treatment group and visit. Observed and change from baseline values will be presented.

9.5. Electrocardiogram

The triplicate ECG parameter values recorded at each timepoint for heart rate, PR interval, QRS duration, QT interval, and QTcF (corrected QT interval using Fridericia's formula) interval will be averaged (and rounded to the nearest whole number) for each subject and timepoint for the purpose of statistical summarization. Additionally, for the triplicate investigator overall categorical assessment (ie, Normal, Abnormal not Clinically Significant, or Abnormal Clinically Significant) at each timepoint, the outcome representing the greatest degree of abnormality will be selected for summarization.

Descriptive statistics for the observed values and changes from baseline will be presented for each of the ECG parameters by timepoint and treatment group.

Frequency tables (number and percentage of subjects) will be presented for the overall categorical assessment at each timepoint.

Two additional categorical summaries (frequency tables displaying number and percentage of subjects) will be presented for the QTcF interval by treatment group. For the first summary, the observed QTcF values at each timepoint will be classified as follows:

- Greater than 450 msec
- Greater than 480 msec
- Greater than 500 msec

For the second categorical summary, the changes from baseline to each subsequent timepoint will be classified as follows:

- Increase greater than 30 msec
- Increase greater than 60 msec

The same categorical summaries will be presented in frequency tables for values at any postdose timepoint (including unscheduled assessments) meeting the aforementioned criteria.

9.6. Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a measure of suicidal ideation and behavior. The C-SSRS data will be presented in the following summaries by treatment group:

- Screening/lifetime assessment
- Baseline assessment
- Postbaseline assessments

Each summary will display the number and percentage of subjects who report “Yes” to specific C-SSRS items or categories of items (a category is assigned a “Yes” value if a “Yes” is reported for any item in the category). These C-SSRS items and categories are as follows:

- Suicidal Ideation Items
  - (1) Wish to be dead
  - (2) Non-specific active suicidal thoughts
  - (3) Active suicidal ideation with any methods (not plan) without intent to act
  - (4) Active suicidal ideation with some intent to act, without specific plan
  - (5) Active suicidal ideation with specific plan and intent
- Suicidal Ideation Category: Any of items (1) through (5)
- Suicidal Behavior Items
  - (6) Preparatory acts or behavior
  - (7) Aborted attempt
  - (8) Interrupted attempt
  - (9) Non-fatal suicide attempt
  - (10) Completed suicide (“Since Last Visit” assessments only)

- Suicidal Behavior Category: Any of items (6) through (10)
- Suicidal Ideation or Behavior Category: Any of items (1) through (10)

For the "all postbaseline assessments" summary, each subject's C-SSRS responses for all postbaseline assessments will be evaluated, and a "Yes" response for any assessment will be considered as a "Yes" for the subject.

In addition to the summaries described above, shift tables comparing postbaseline suicidal ideation scores to baseline scores will be presented. The shift table scores are defined as the following:

0 = No suicidal ideation
1 = Wish to be dead
2 = Non-specific active suicidal thoughts
3 = Active suicidal ideation with any methods (not plan) without intent to act
4 = Active suicidal ideation with some intent to act, without specific plan
5 = Active suicidal ideation with specific plan and intent

The shift tables will display the number and percentage of subjects within each cell of a 6 x 6 table for each treatment group, with the rows representing the baseline score and the columns representing the maximum score recorded across all postbaseline assessments (including both scheduled and unscheduled visits). Subjects missing either a baseline score or all postbaseline scores will not appear in the table.

10. PERFORMANCE QUALIFICATION OF SAS® PROGRAMS

The analysis and summary of data from this study will be performed using SAS® 9.4 (or a later release if available). All SAS® programs used in the production of statistical analyses, tables, listings, and figures described in this SAP will undergo performance qualification (verification that the program produces the intended output) in accordance with department standard operating procedures. The performance qualification may include independent programming and/or peer review of the SAS® log files. In addition, tables, figures, listings, and statistical analysis output will be independently reviewed for completeness and accuracy.

11. [redacted]

[redacted]

12. REFERENCES

European Medicines Agency. Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials. March 2020.

United States Food and Drug and Administration. Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency. Guidance for Industry, Investigators, and Institutional Review Boards. March 2020, updated January 2021.

Signature Page for VV-TMF-45790 v1.0

Reason for signing: Approved	Name: [redacted] Role: Biostatistics Date of signature: 19-Nov-2022 00:16:57 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Biostatistics Date of signature: 19-Nov-2022 01:42:24 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Clinical Development Date of signature: 21-Nov-2022 18:43:34 GMT+0000

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