1.0 TITLE PAGE

[redacted]

MT10109L-005

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of MT10109L (NivobotulinumtoxinA) for the Treatment of Glabellar Lines with or without Concurrent Treatment of Lateral Canthal Lines

STATISTICAL ANALYSIS PLAN - Clinical Study Report

[Final]: [18 NOV 2020]

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse events of special interest
ALT	Alanine Aminotransferase
ANCOVA	analysis of covariance
AST	Aspartate Aminotransferase
CMH	Cochran-Mantel-Haenszel
CRF	case report form
ECG	electrocardiogram, electrocardiographic
EU	European Union
eCRF	electronic case report form
FLO-11	Facial Line Outcomes Questionnaire
FLSQ	Facial Line Satisfaction Questionnaire
FWS	Facial Wrinkle Scale
GL	glabellar lines
ITT	intent to treat
LCL	lateral canthal lines
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
PDSOT	possible distant spread of toxin
Q1	25^{th} percentile
Q3	75^{th} percentile
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{½}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{⅓}$)
RBC	Red blood cell

SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SI	*Le Système International d'Unités* (International System of Units)
TEAE	treatment-emergent adverse event
UFL	upper facial line
WBC	White blood cell

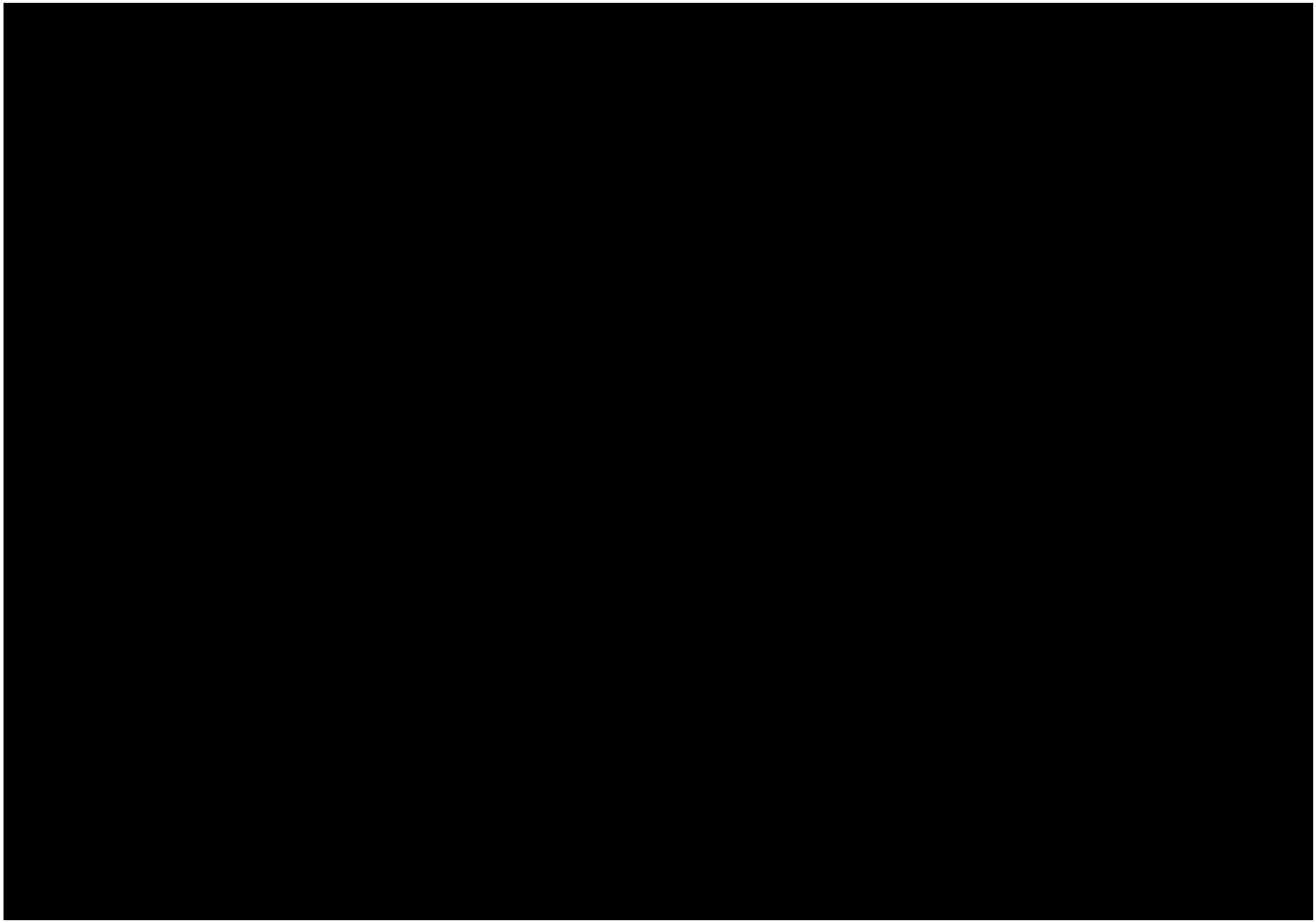
4.0 INTRODUCTION

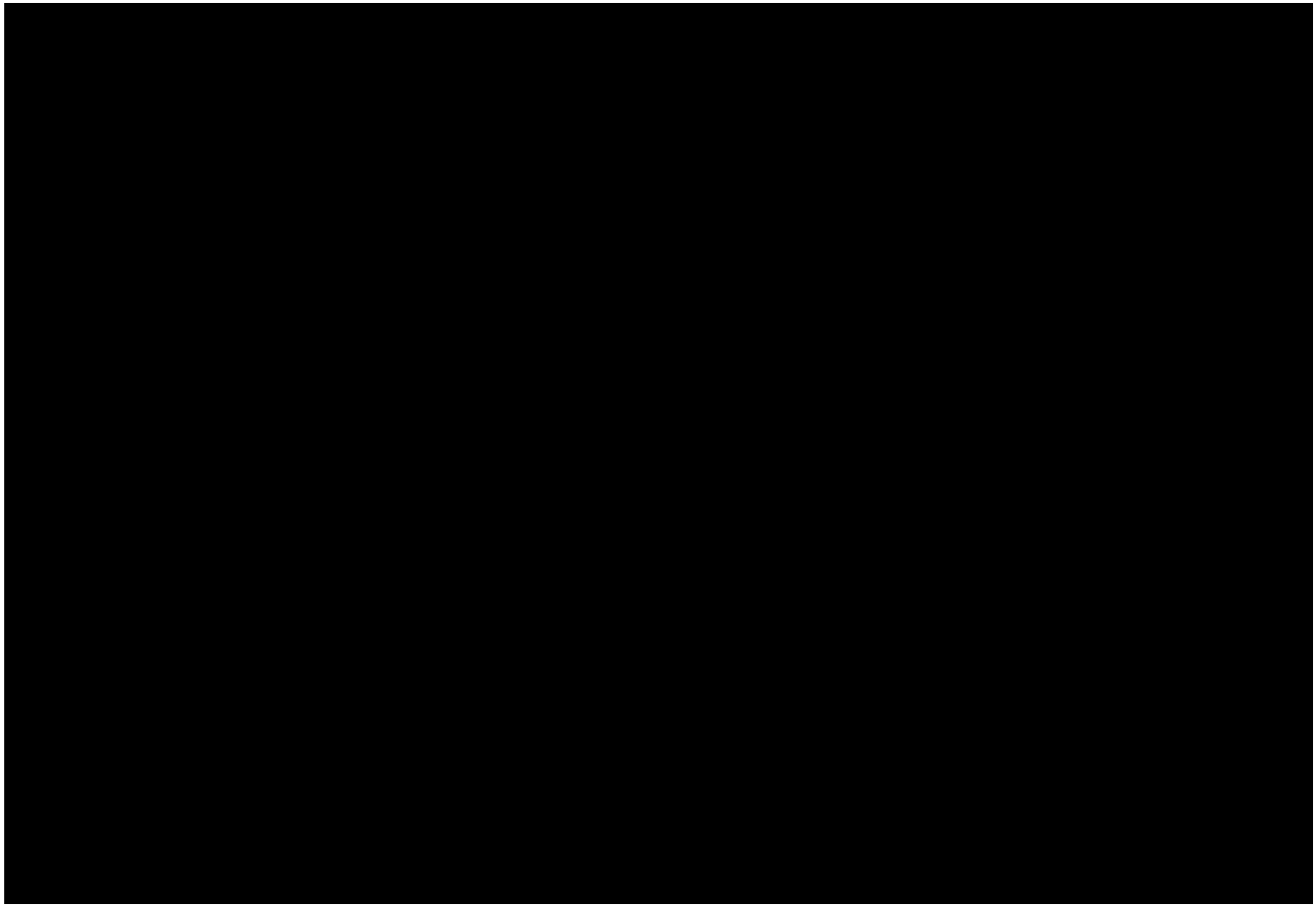
This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the final protocol amendment of Study MT10109L-005 (version dated Oct 2020). Specifications of tables, figures, and data listings are contained in a separate document.

Study MT10109L-005 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Participants are adults at least 18 years of age with moderate to severe glabellar lines (GL) at maximum frown and Lateral Canthal Lines (LCL) at maximum smile. The severity of GL and LCL will be assessed based on Facial Wrinkle Scale (FWS) scores, ranging from none (0) to severe (3).

The length of this study will be approximately 12 months. [redacted]

After the first treatment on Day 1, all participants will be evaluated for safety and efficacy at follow-up visits occurring on Day 7, 14, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360. Participants can receive a retreatment (Treatment 2) of MT10109L 20 U, 44 U, or placebo if retreatment criteria are met at the Day 180 visit. [redacted]





5.0 OBJECTIVES

The objectives of this study are to evaluate the safety and efficacy of MT10109L versus placebo in the treatment of participants of GL with or without concurrent treatment of LCL.

6.0 PARTICIPANT POPULATIONS

6.1 INTENT-TO-TREAT POPULATION

The intent-to-treat (ITT) Population will consist of all randomized participants. Efficacy analyses for US FDA will be based on the ITT population.

[redacted]

6.3 SAFETY POPULATION

The safety population will consist of all participants who received at least 1 injection of study intervention.

7.0 PARTICIPANT DISPOSITION

The number and percentage of participants in the 3 study populations (ITT, [redacted] safety) will be summarized by treatment group and overall; the number of participants screened and randomized will be summarized by study center.

The number of participants screened will be summarized overall. The number and percentage of participants who were randomized, treated, or who completed the study and prematurely discontinued will be presented for each treatment group and pooled across treatment groups. A frequency table showing participant disposition (continuing, entered to the next cycle, completed, discontinued) will also be provided for all analysis populations for each treatment cycle.

Tabulation of the numbers and percentages of participants in each exit status category (i.e., adverse event, pregnancy, lost to follow-up, personal reasons, protocol violations and other) will be provided for each treatment group for entire study and by treatment cycle for all analysis populations. Discontinued participants will be listed along with the corresponding reason(s) for early withdrawal from the study.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters and baseline characteristics will be summarized by treatment group for ITT [redacted]. Continuous variables will be summarized by number of participants and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

Demographic parameters include age, age group (< 65 and ≥ 65), race, ethnicity and sex.

Baseline characteristics include weight, height, body mass index (BMI, calculated as weight [kg]/ height[m]^2), FWS scores of GL severity at maximum frown and at rest (assessed by investigators and participants), LCL severity at maximum smile and rest (assessed by investigators only), [redacted]. The distribution of the baseline characteristics will be summarized by treatment group.

The number and percentage of participants with abnormalities in medical and surgical histories in each system organ class (SOC) and preferred term (PT) will be summarized by treatment group for the ITT population.

Prior medications include all medications taken any time prior to the Day 1 baseline visit, whether or not medication is continuing beyond the Baseline Visit.

Concomitant medications encompass all medicinal products that the participant was taking prior to the Day 1 baseline visit which are ongoing at the visit, in addition to all medications that have a start date on or after the Day 1 visit date.

WHODrug Global B3 202003 will be used to classify prior and concomitant medications by therapeutic class and drug name.

Both prior and concomitant medications will be coded by drug name and therapeutic class. The use of prior and concomitant medications will be summarized by drug class and drug name in each treatment group for the ITT [redacted].

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 EXTENT OF EXPOSURE

Participants' exposure to study intervention will be summarized by total duration of treatment exposure and by cycle [redacted] and by number of treatments received.

10.0 EFFICACY ANALYSES

For US FDA, the primary and secondary efficacy analyses will be based on the ITT population. For EU regulatory agencies, the primary and secondary efficacy analyses will be based on the mITT population. Other efficacy analyses will be based on the ITT population.

Missing values for the primary measures will be imputed using multiple imputation methods up to Day 180 for Treatment Cycle 1. [redacted]

The evaluation of the equality of the proportions of responders will be based on Cochran-Mantel-Haenszel (CMH) test stratified by investigator-assessed baseline GL severity at maximum frown. [redacted]

10.1 PRIMARY EFFICACY PARAMETER(S)

US FDA

For US FDA, the composite primary efficacy endpoint is the proportion of participants with a $\geq$ 2-grade improvement from baseline on the FWS according to both the investigator- and participant-rated assessments of GL severity at maximum frown at Day 30 of Treatment Cycle 1.

The primary analysis will be performed on the ITT population.

The following hypothesis will be used to compare the MT10109L groups with placebo:

- Null hypothesis: MT10109L 20 U and placebo are equally effective in reducing GL severity at maximum frown as measured by the proportion of responders with a ≥ 2-grade improvement from baseline based on both the investigator-rated and participant-rated FWS at Day 30 of Treatment Cycle 1.

- Alternative hypothesis: MT10109L 20 U and placebo are not equally effective in reducing GL severity at maximum frown as measured by the proportion of responders with a ≥ 2-grade improvement from baseline based on both the investigator-rated and participant-rated FWS at Day 30 of Treatment Cycle 1.

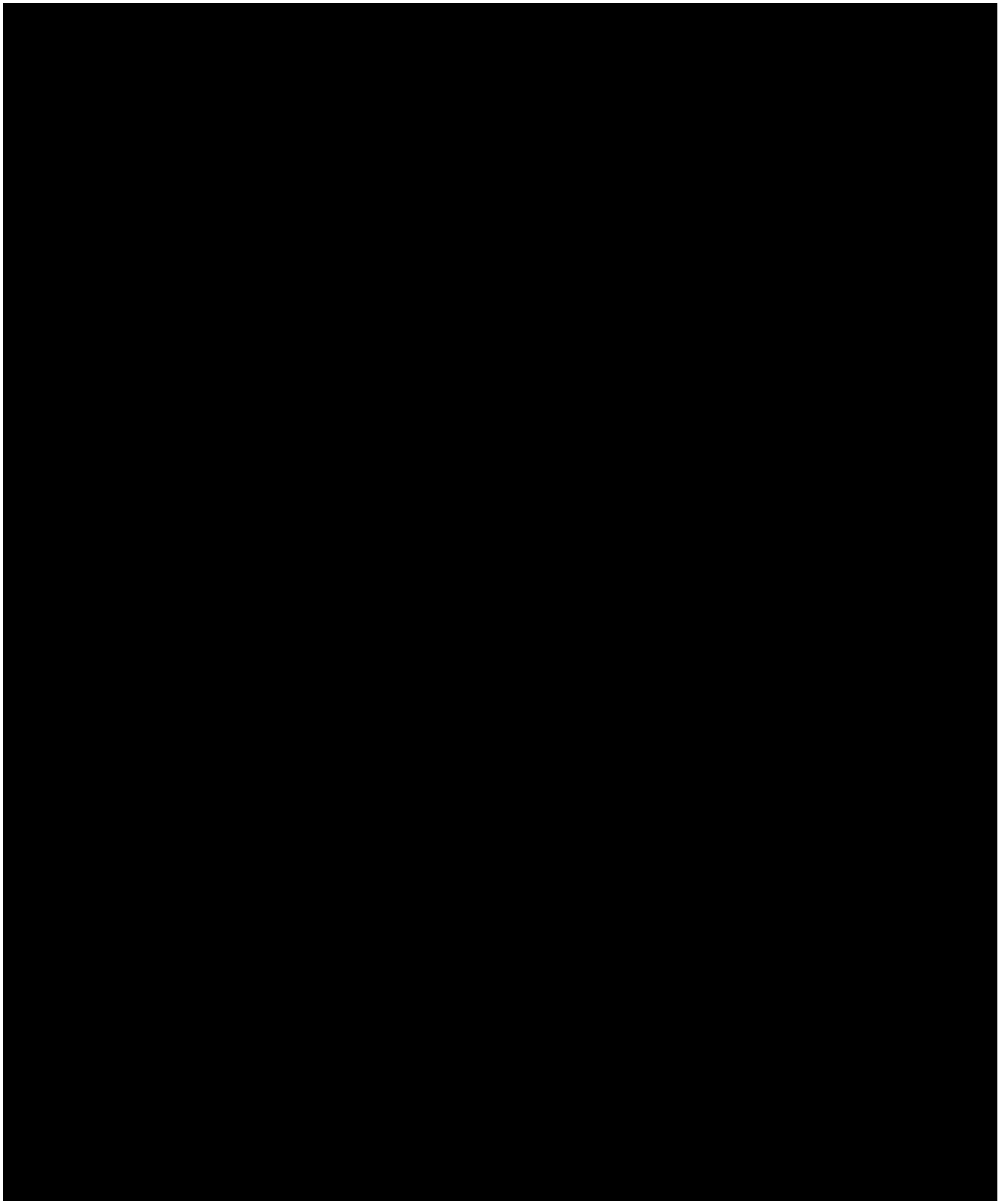
[redacted]

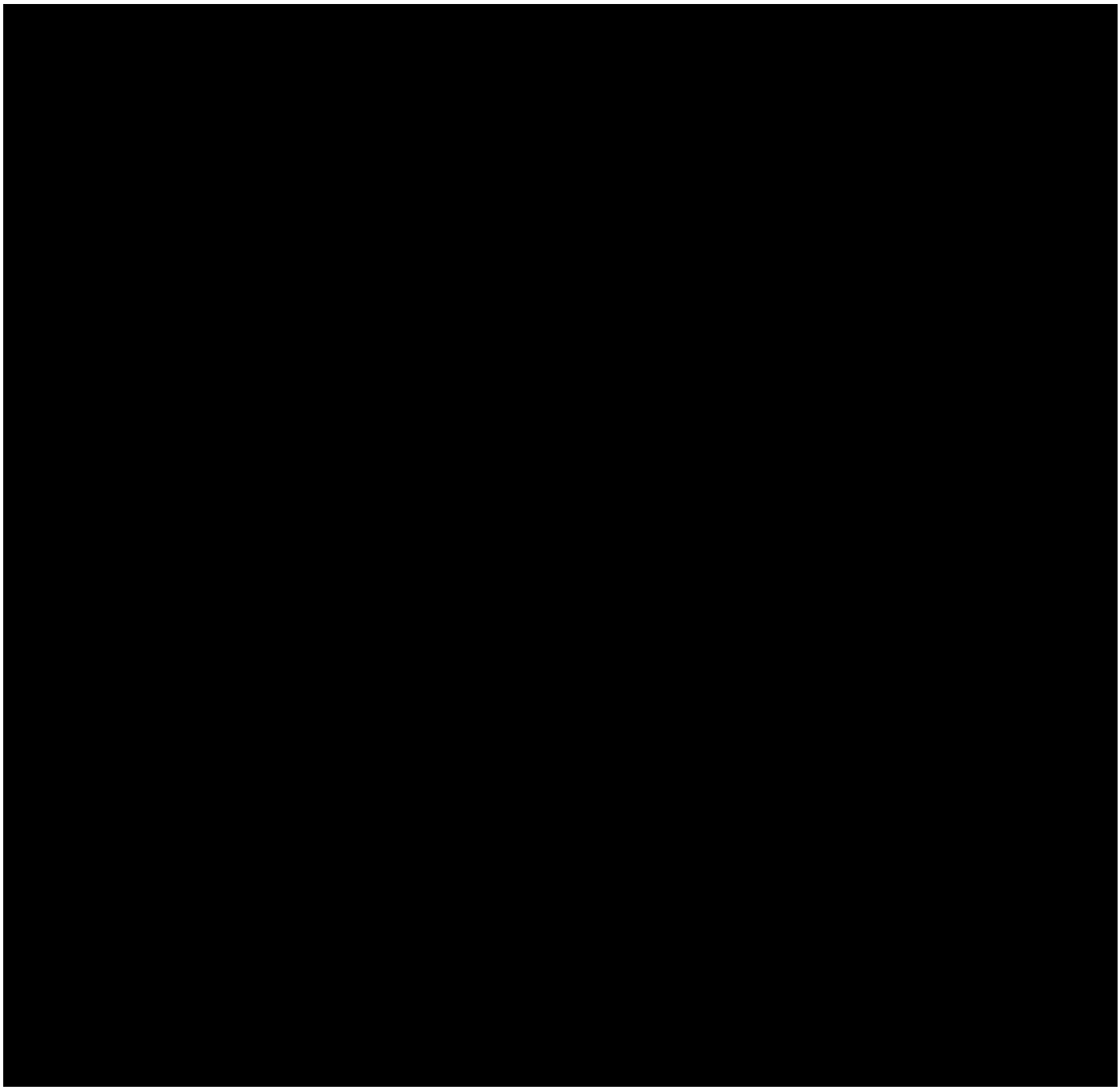
[redacted]

[redacted]

Analyses of the secondary efficacy variables will be performed for all study visits using observed data, with the primary time-point at Day 30 of the Treatment Cycle 1 [redacted]

[redacted]





11.0 SAFETY ANALYSES

The safety analysis will be performed using the safety population. The safety parameters will include adverse events (AEs), [redacted] vital signs, Electrocardiogram (ECG), Hematology and Chemistry laboratory and immunogenicity analyses. For each safety parameter of the vital sign, ECG, Hematology and Chemistry laboratory parameters, the last non-missing safety assessment before the first dose of study intervention will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of participants and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

11.1 ADVERSE EVENTS

AEs will be coded from the verbatim text into preferred term (PT) and the primary system organ class (SOC) by using the MedDRA dictionary. In general, adverse events (AEs) data will be analyzed and presented for:

1. TEAEs: An adverse event will be considered a treatment-emergent adverse event (TEAE) if: 1) The adverse event began on or after the date of the first study intervention; or 2) The adverse event was present before the date of the first study intervention, but increased in severity or became serious on or after the date of the first study intervention. An adverse event that occurs more than 30 days after the study exit will not be counted as a TEAE.

[redacted]

Per case report form instructions, a new AE record will be created with a new AE onset date for any AE that worsens. Therefore, TEAEs can simply be identified as those AEs with a recorded onset date on or after the date of the first study intervention and within 30 days after the study exit.

In each of the analysis periods (entire study, or by treatment cycle), a specific TEAE will only count once per participant, associated with its worst severity during the time period of interest. Unless stated otherwise, the method of analyses described in this section will be applied to each of the screening/baseline and study intervention periods.

Adverse events will be summarized by treatment group for the entire study and by treatment cycle in descending order of incidence rate.

Three incidence rate tables will be presented for summarizing all TEAEs:

1) by descending order of incidence rate
2) by primary SOC and PT
3) by SOC, PT, and severity.

Serious TEAE and treatment-related TEAE will be summarized by primary SOC and PT for entire study. Treatment-related TEAE will also be summarized by related to study drug or related to study procedure. TEAE leading to study discontinuation will be summarized by primary SOC and PT for entire study [redacted]

A participant listing will be generated for all AEs, SAEs, treatment-related AEs and AEs leading to study discontinuation.

[redacted] All AEs associated with PDSOT will be tabulated by SOC, PT, and treatment group; in addition, all PDSOT AEs will be listed by participant. [redacted]

[redacted]

[redacted]

11.2 CLINICAL LABORATORY PARAMETERS

Study baseline is defined to be the data measured before dosing on Day 1. Descriptive statistics (n, mean, standard deviation, minimum, median, and maximum) for clinical laboratory values at baseline, and change from baseline at post-baseline visits will be summarized, in SI units (System of International Units), for all continuous clinical laboratory parameters specified below.

The clinical laboratory parameters include the following:

Hematology:	Hemoglobin, hematocrit, red blood cell count (RBC), RBC morphology, white blood cell count (WBC), neutrophils, lymphocytes, monocytes, basophils, eosonophils, and platelets

Blood Chemistry: glucose, creatinine, urea nitrogen, total bilirubin, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, uric acid, sodium, potassium, bicarbonate (carbon dioxide content), chloride, phosphorus, calcium, magnesium, and total protein.

11.3 VITAL SIGNS

Study baseline is defined to be the data measured before dosing on Day 1. Baseline and change from study baseline data on blood pressure (mm Hg), pulse rate (beats/min) and respirations (breaths per minute) will be summarized as descriptive statistics for each time point and each visit for each treatment group.

11.4 ELECTROCARDIOGRAM

Descriptive statistics for ECG parameters (eg, heart rate, PR interval, RR interval, QRS duration, QT interval, corrected QT [QTc] intervals) at baseline, and changes from baseline at all post-baseline timepoints will be presented for all participants in the Safety Population. For each parameter, only participants who had both baseline post-baseline assessments will be included in the summary. [redacted]

Data listings which include ECG basic parameters and ECG abnormalities will be produced.

[redacted]

11.7 PREGNANCY TESTS

Urine pregnancy tests are performed prior to treatment and at exit visit for females of childbearing potential. Participants with positive pregnancy test results will be listed by treatment group, including urine sample collection date, and days since most recent treatment.

11.8 IMPACT DUE TO COVID-19

Participants discontinued related to COVID-19 will be listed.

The description of impact to visit assessment due to COVID-19 (missed, remote audio visit, etc.) will be listed.

For participants affected by COVID-19, their COVID-19 status, COVID-19 supplemental signs and symptoms will be listed.

12.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

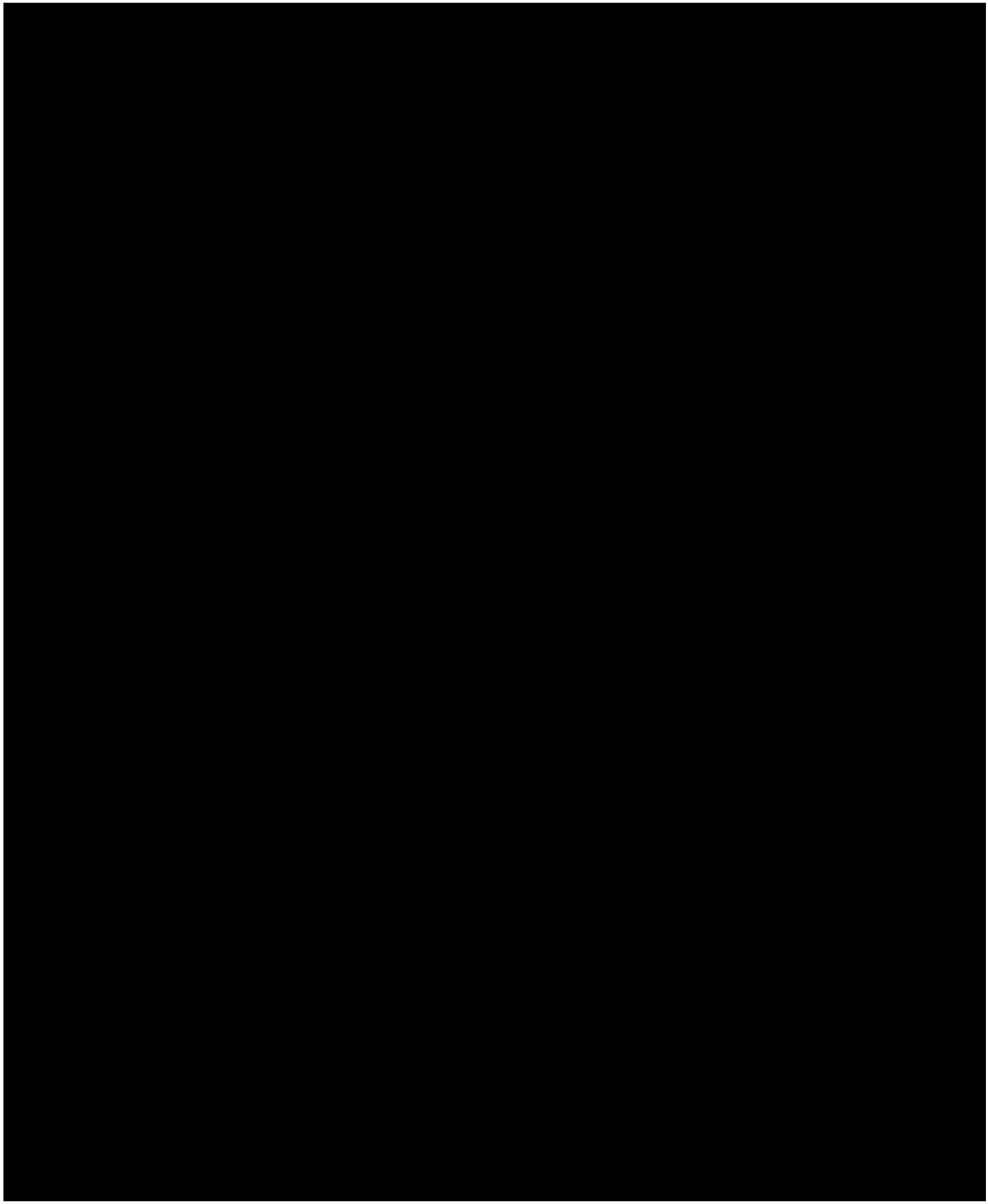
13.0 DETERMINATION OF SAMPLE SIZE

Approximately 375 participants will be randomized [redacted]

[redacted]

14.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.3 (or newer) of SAS on a Linux operating system.

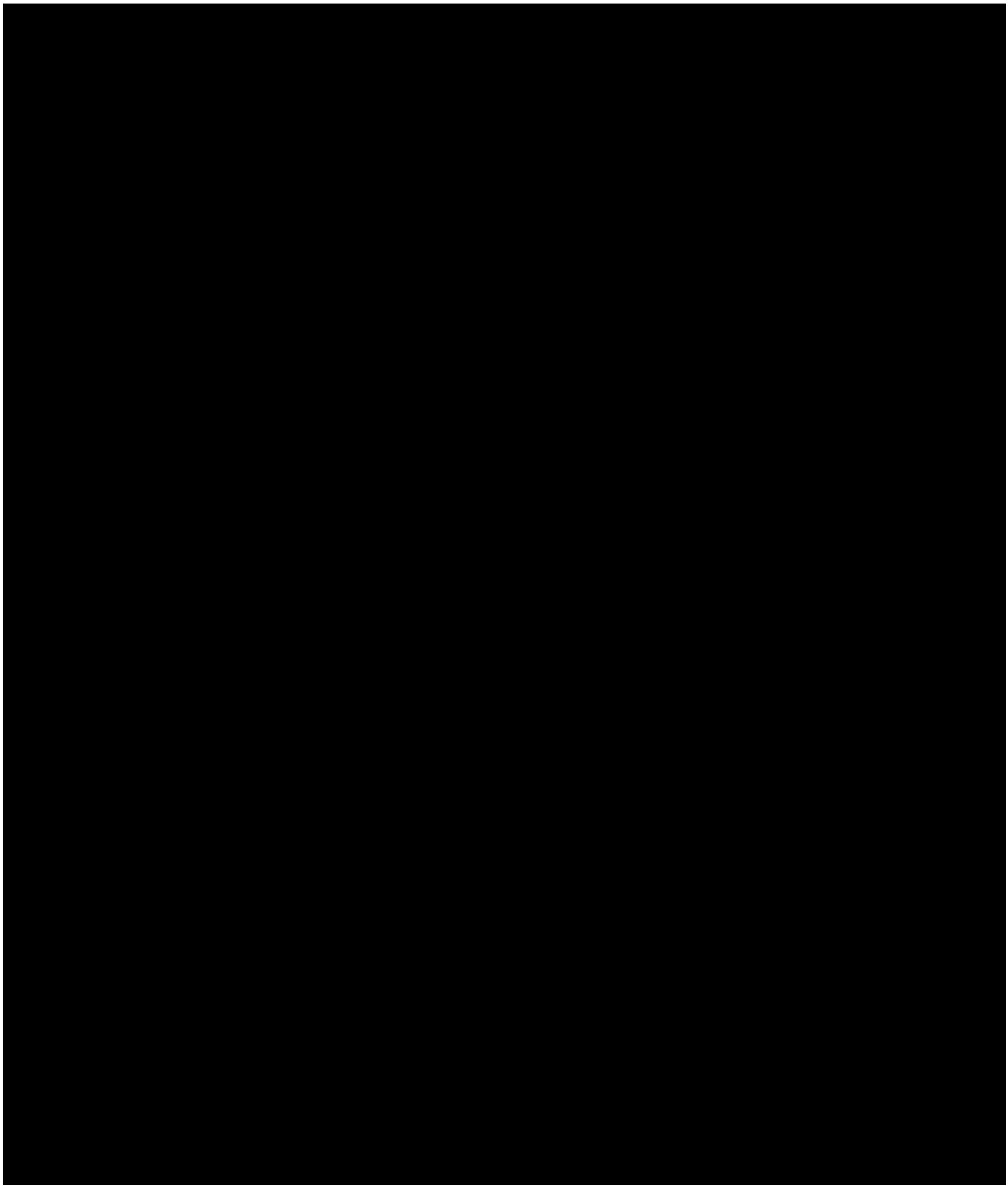


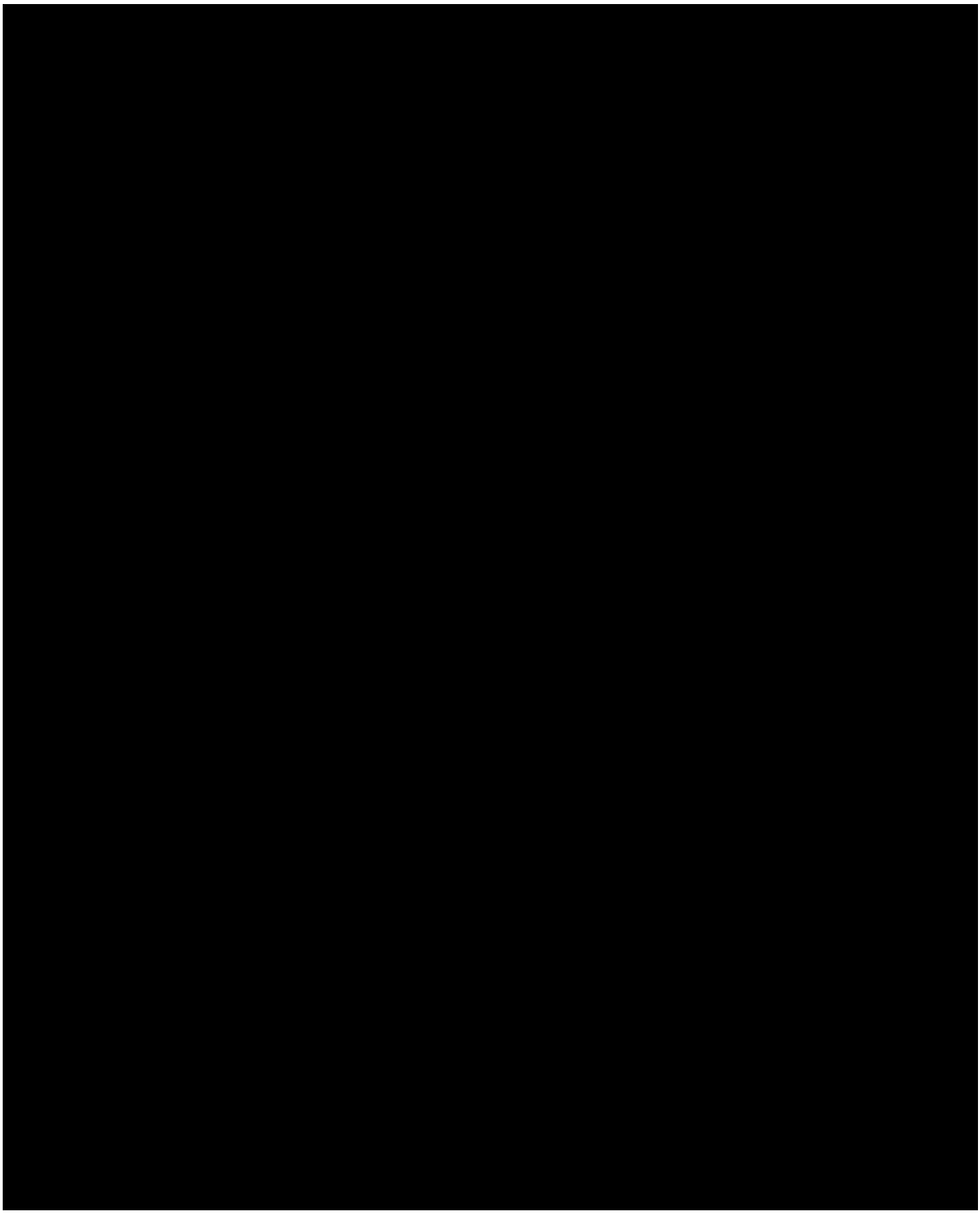
[redacted]

If there are values from multiple visits in a given window, the value collected from the visit closest to the target day will be used [redacted]

[redacted]

[redacted]





[redacted]

15.5 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a participant has repeated assessments before the start of the first treatment, the results from the final nonmissing assessment made prior to the start of the study intervention will be used as baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last nonmissing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics.

15.6 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of study intervention, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study intervention, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

15.7 MISSING CAUSAL RELATIONSHIP TO STUDY INTERVENTION FOR ADVERSE EVENTS

If the causal relationship to the study intervention is missing for an AE that started on or after the date of the first dose of study intervention , a causality of yes will be assigned. The imputed values for causal relationship to study intervention will be used for the incidence summary; the values will be shown as missing in the data listings.

15.8 MISSING DATE INFORMATION FOR ADVERSE EVENTS

Partial adverse event onset date will be imputed as follows: 1) if day is missing but month is not, impute the date as the first day of the month; 2) if both day and month are missing, impute the date as 01 Jan; 3) if imputed onset date is before the first treatment, yet the corresponding adverse event was not observed pre-treatment, then impute the onset date as the first treatment date. Imputed partial adverse event onset date will only be used to determine the adverse event onset cycle.

Other partial adverse event dates will not be imputed. All partial dates will be listed “as is” in the data listings.

15.9 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

There will be no imputation for missing or partially reported medication start and/or end dates. However, reported partial information will be utilized in classification of prior and concomitant medications, when appropriate. For example, a medication may be classified as a pre-study medication if the partial end date provided is determined to definitively have occurred prior to the study intervention date (for example, the partial end date provided is “2017”, and Day 1 occurred on August 29, 2018).

If start and/or stop dates for medications are only partially reported but can be classified as having occurred prior to Day 1, then the medications will be included in this summary of prior medications.

If stop dates for medications are only partially reported and cannot be definitively classified as having occurred prior to Day 1, then the medications will be included in this summary of concomitant medications.

17.0 REFERENCES

Dmitrienko A, Molenberghs G, Chuang-Stein C, Offen W. Gatekeeping strategies. In: Analysis of clinical trials using SAS: a practical guide. Cary, NC: SAS Institute; 2005. p. 104-108.

O'Kelly M, Ratitch B. Clinical trials with missing data: A guide for practitioner. Statistics in Practice. Wiley;2014.

Wilson EB, Hilferty, MM. The distribution of chi-squared. Proceedings of the National Academy of Sciences, Washington. 1931;17:12,684-688.

18.0 HISTORY OF CHANGES

Amendment 1:

Date	Section(s)	Description
11/1/2020	3.0	Added abbreviation AESI.
11/18/2020	4.0	Changed to base on protocol amendment dated Oct 2020.
11/1/2020	7.0	Deleted word "cumulative" to remove confusion.
11/1/2020	[redacted]	[redacted]
11/1/2020	11.1	Added summary for AESI.
11/1/2020	11.8	Added "Impact due to COVID-19" section.
11/1/2020	[redacted]	[redacted]
11/1/2020	15.2	Added data step in a specific scenario when value is not in range after iteration when conducting [redacted] Revised typo "BOTOX" to "MT10109L". [redacted]
11/1/2020	15.4	Added detail about the calculation [redacted]
11/18/2020	16.0	Added [redacted]
11/18/2020	17.0	Added references.

Electronic Signatures