1.0 TITLE PAGE

MT10109L-002

A Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study to Evaluate the Safety and Efficacy of MT10109L (NivobotulinumtoxinA) for the Treatment of Lateral Canthal Lines

STATISTICAL ANALYSIS PLAN - Clinical Study Report

[Final]: [18 NOV 2020]

[redacted]

[redacted]

3.0 LIST OF ABBREVIATIONS

AE	adverse event
[redacted]	[redacted]
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
CMH	Cochran-Mantel-Haenszel
ECG	electrocardiogram
EU	European Union
[redacted]	[redacted]
[redacted]	[redacted]
FWS	Facial Wrinkle Scale with Photonumeric Guide
ITT	intent to treat
LCL	lateral canthal lines
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
Q1	25th percentile
Q3	75th percentile
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
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
WBC	white blood cell

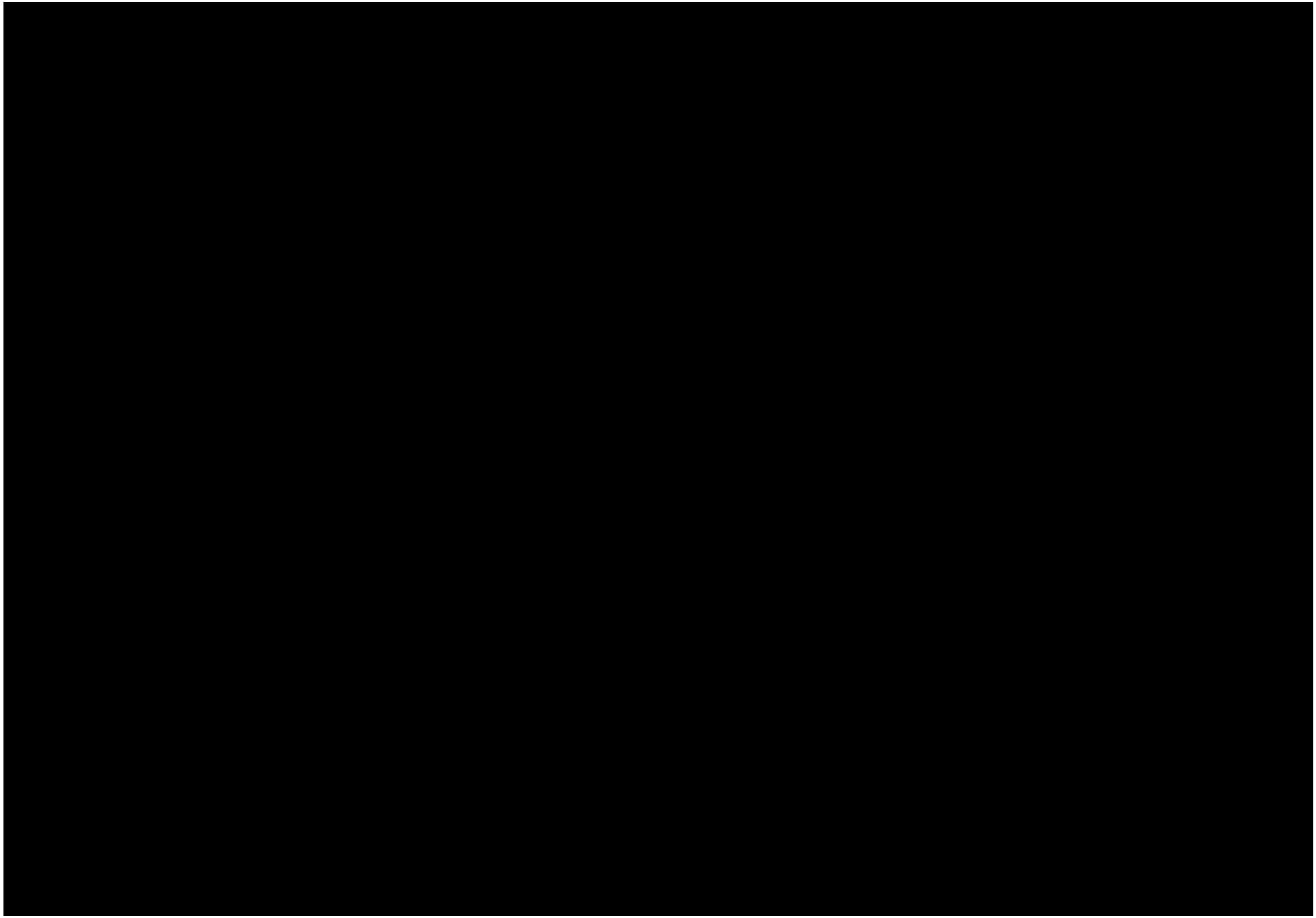
4.0 INTRODUCTION

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-002 (dated Oct 2020). Specifications of tables, figures, and data listings are contained in a separate document.

Study MT10109L-002 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study conducted across approximately 16 global sites to evaluate the safety and efficacy of MT10109L in treating lateral canthal lines (LCL). [redacted] Participants are adults ≥ 18 years of age [redacted]

The total duration of study participation for each participant is 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 Days 7, 14 after each intervention and on 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, and 360. [redacted]



[redacted]

5.0 OBJECTIVES

The objectives of this study are to evaluate the safety and efficacy between MT10109L and placebo in the treatment of participants with moderate to severe LCL.

6.0 PARTICIPANT POPULATIONS

6.1 INTENT-TO-TREAT POPULATION

The Intent-to-Treat (ITT) Population will consist of all randomized participants. Primary and secondary efficacy analyses for the US FDA will be performed 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. The safety analyses will be based on the safety population. All safety analyses will be performed with participants by their actual intervention received.

7.0 PARTICIPANT DISPOSITION

The number and percentage of participants [redacted] will be summarized by treatment group and overall; the number of participants screened will be summarized overall 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 [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 LCL severity at maximum smile and rest (assessed by investigators and participants), [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 population.

9.0 EXTENT OF EXPOSURE

Participants' exposure to study intervention will be summarized by total duration of treatment exposure and by cycle [redacted] In addition, for the entire study, the number and percentage of participants receiving 1, 2, or 3 study interventions will be summarized.

[redacted]

10.1 PRIMARY EFFICACY PARAMETERS

US FDA

For the FDA, the composite efficacy endpoints are the proportion of participants with a ≥ 2-grade improvement from baseline on the FWS according to both investigator and participant assessments of LCL severity at maximum smile at Day 30 of Treatment Cycle 1 after a single IM injection of MT10109L or placebo in the LCL.

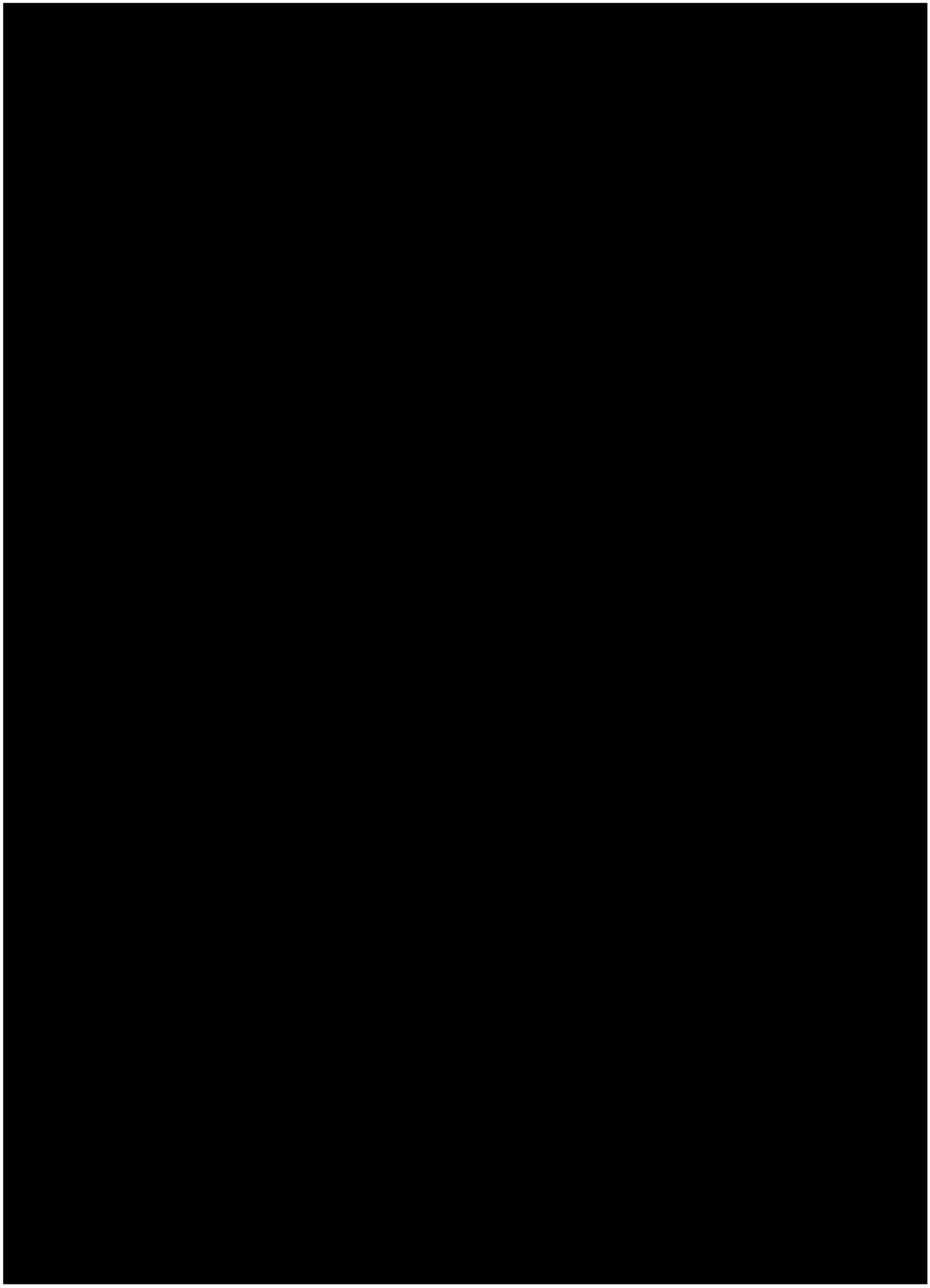
The primary analysis will be performed on the ITT population.

The following hypotheses will be used to compare MT10109L 24 U with placebo:

- Null hypothesis: MT10109L 24 U and placebo are equally effective in reducing LCL severity at maximum smile as measured by the proportion of responders with a ≥ 2-grade improvement from baseline based on both the investigator- and participant-rated FWS at Day 30 of Treatment Cycle 1.
- Alternative hypothesis: MT10109L 24 U and placebo are not equally effective in reducing LCL severity at maximum smile as measured by the proportion of responders with a ≥ 2-grade improvement from baseline based on both the investigator- and participant-rated FWS at Day 30 of Treatment Cycle 1.

[redacted]

[redacted]



[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] sign, electrocardiographic (ECG), and Immunogenicity analyses. For each safety parameter of the vital sign and ECG parameters, the last non-missing safety assessment before the first dose of study treatment 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 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 MT10109L 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 treatment periods.

Adverse events will be summarized by treatment group for the entire study and by MT10109L cycle in descending order of incidence rate. [redacted]

[redacted]

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.

[redacted]

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

[redacted]

[redacted]

11.2 CLINICAL LABORATORY PARAMETERS

Hematology and non-fasting blood chemistry assays will be collected at screening visit only and performed by a central laboratory. 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

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

A participant level listing for hematology and blood chemistry will be provided.

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 [redacted] 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.

[redacted]

12.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

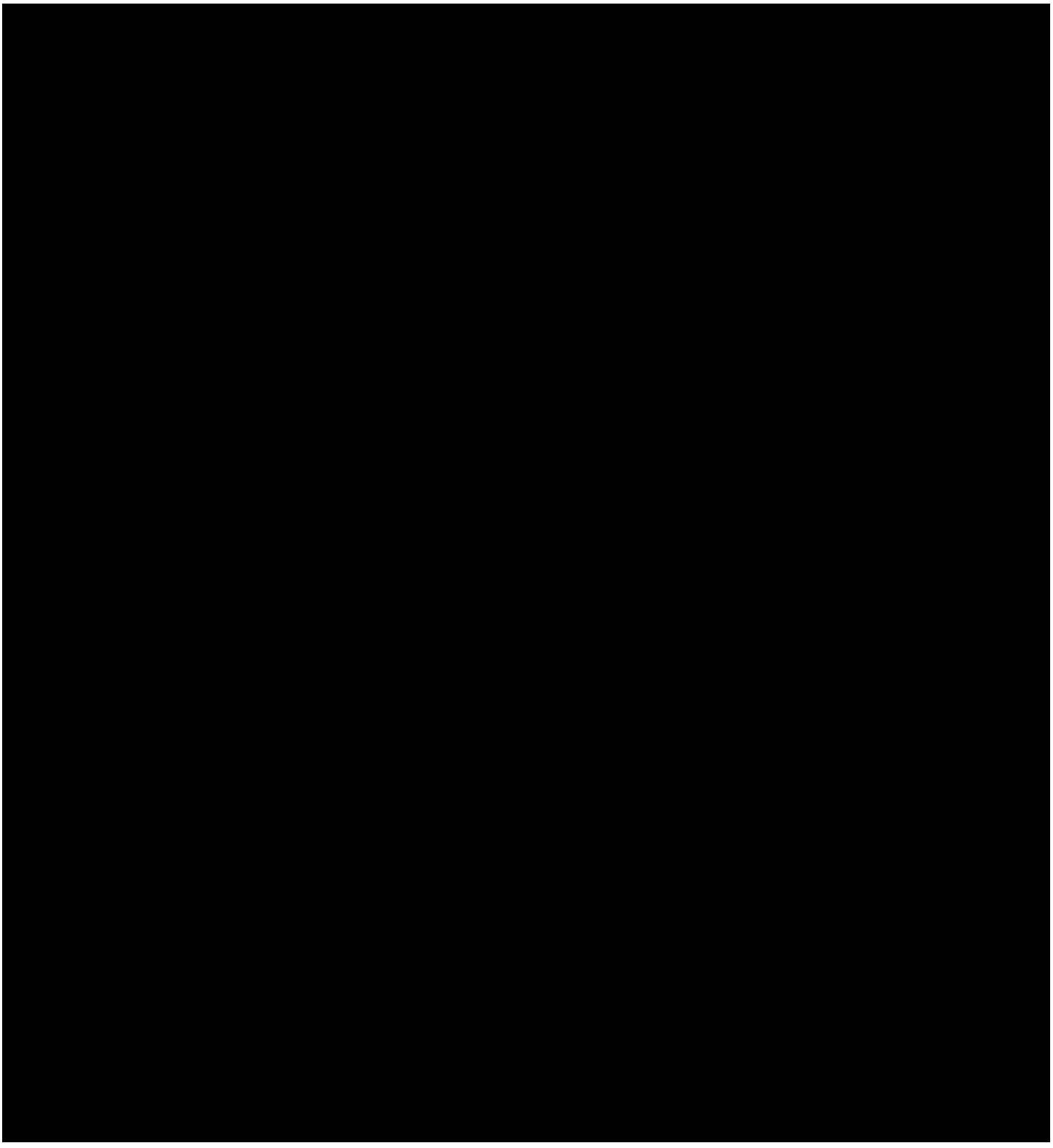
13.0 DETERMINATION OF SAMPLE SIZE

Approximately 225 participants will be randomized [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]

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 treatment 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 treatment, 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 treatment, 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 treatment, a causality of yes will be assigned. The imputed values for causal relationship to study treatment 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 treatment 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.

[redacted].

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.

Electronic Signatures

User	Date	Justification
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]