Title Page

Protocol Title: A Multicenter, Long-term, Open-label Study to Evaluate the Safety of MT10109L (NivobotulinumtoxinA) for the Treatment of Glabellar Lines and Lateral Canthal Lines

Protocol Number: MT10109L-004

Compound Number: MT10109L (NivobotulinumtoxinA)

Short Title: MT10109L in the Long-term, Open-label Treatment of Glabellar Lines and Lateral Canthal Lines

Version: Amendment 1 Version 2.0

Sponsor Name and Legal Registered Address:
Medytox Inc.
[redacted]

Regulatory Agency Identifier Number(s)

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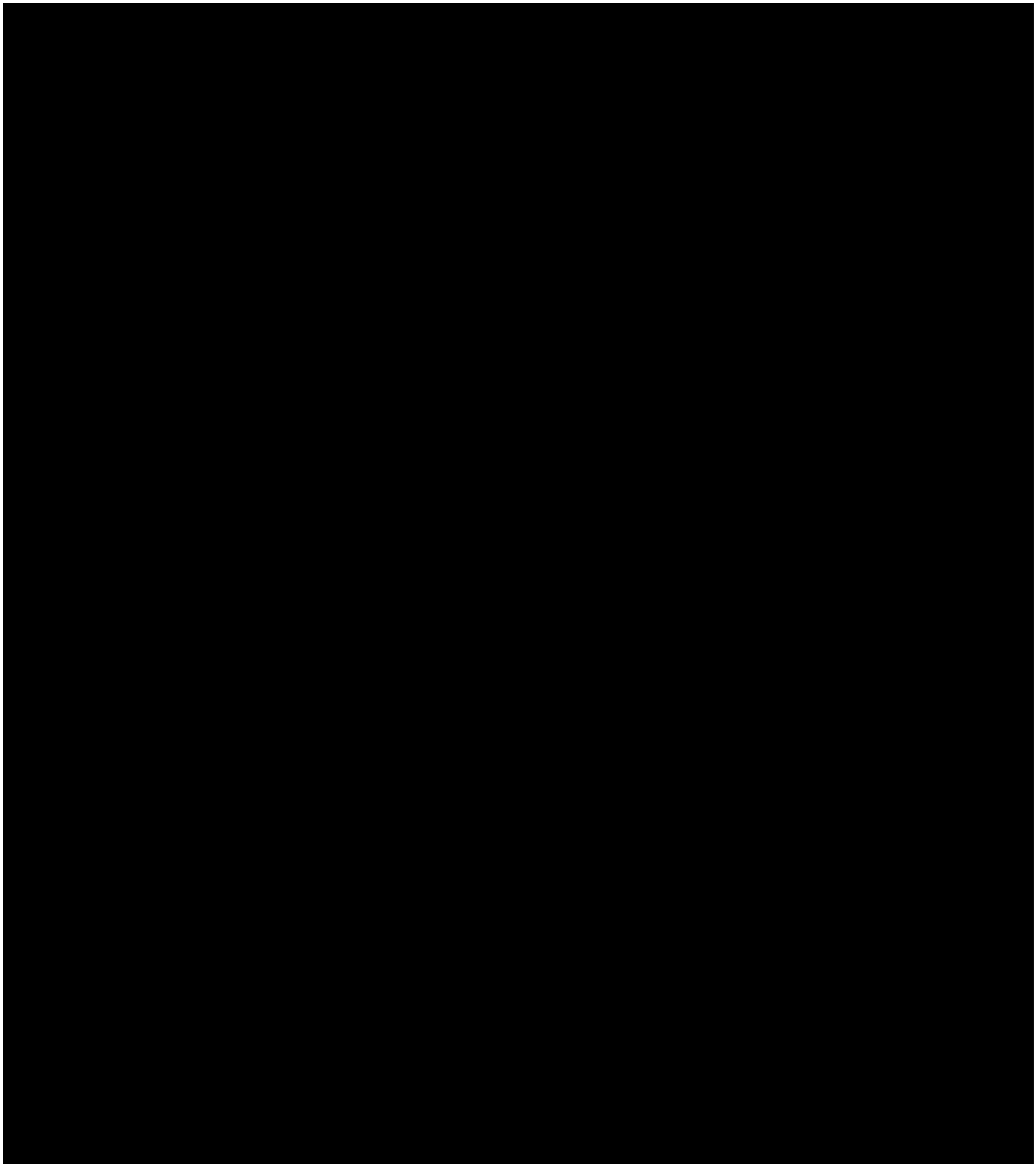

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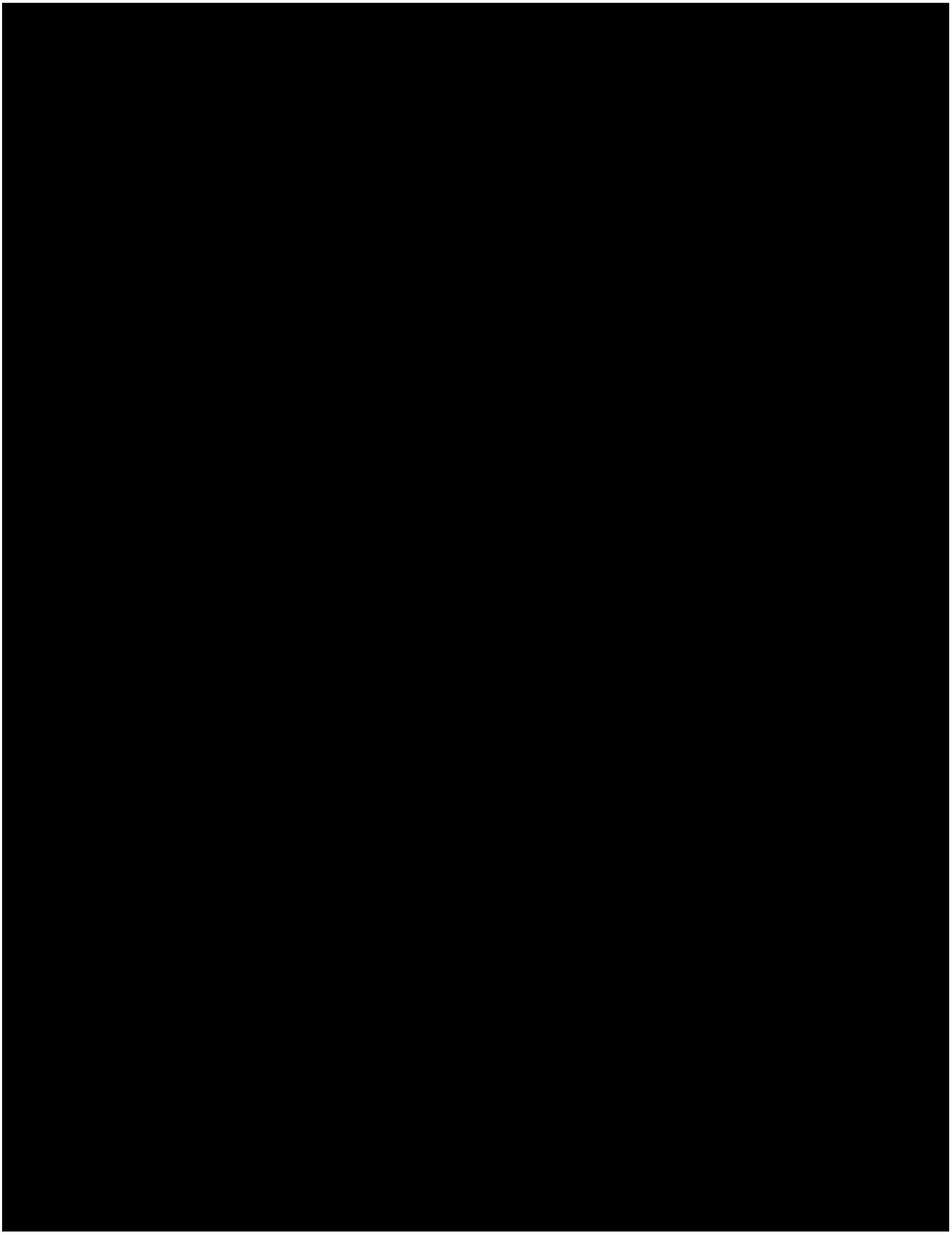


1. Introduction

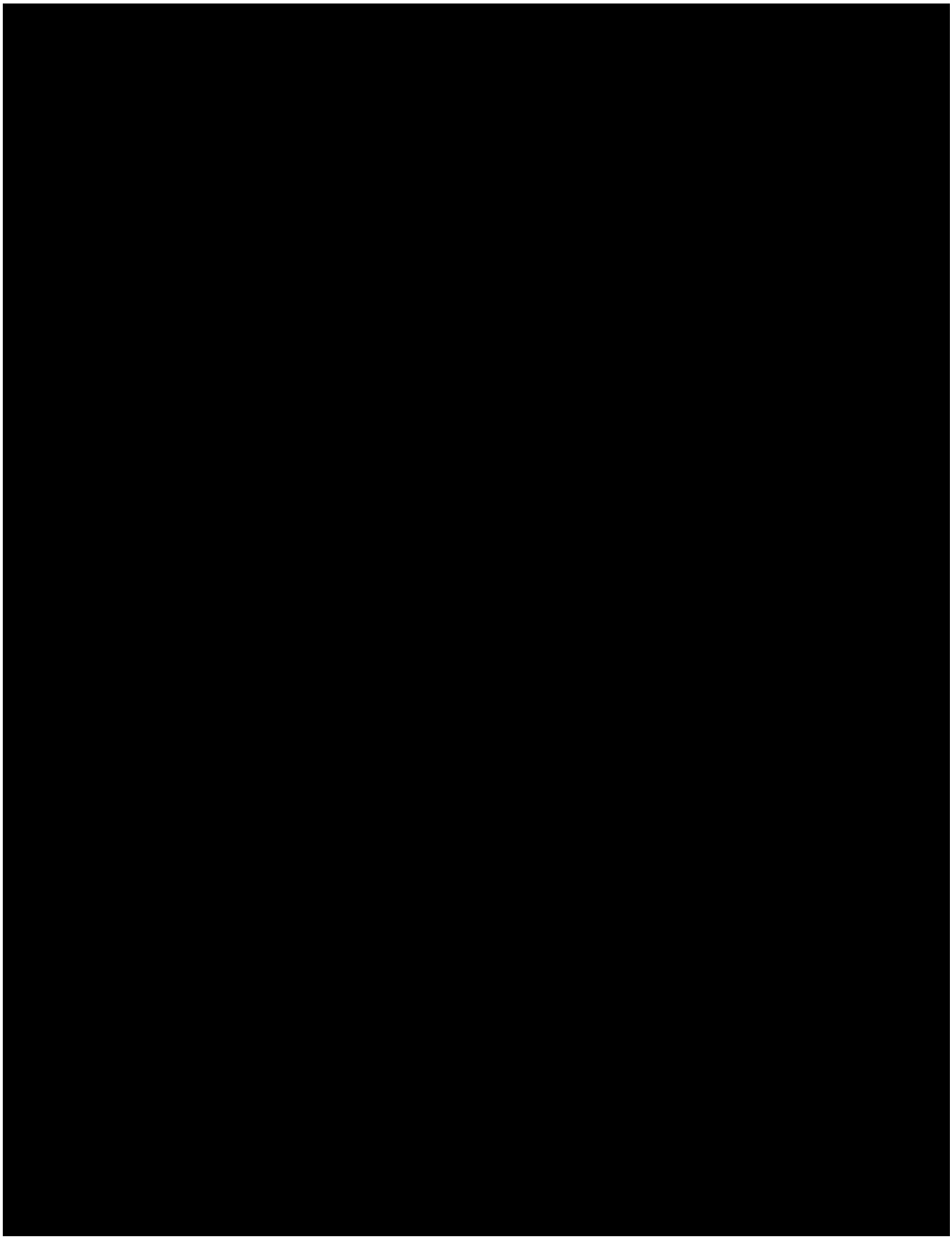
Study MT10109L-004 is an open-label extension of Studies MT10109L-001, -002, -005, and -006 evaluating long term safety of MT10109L. This statistical analysis plan provides an expanded and detailed description of the statistical methods presented in the most recent [redacted]

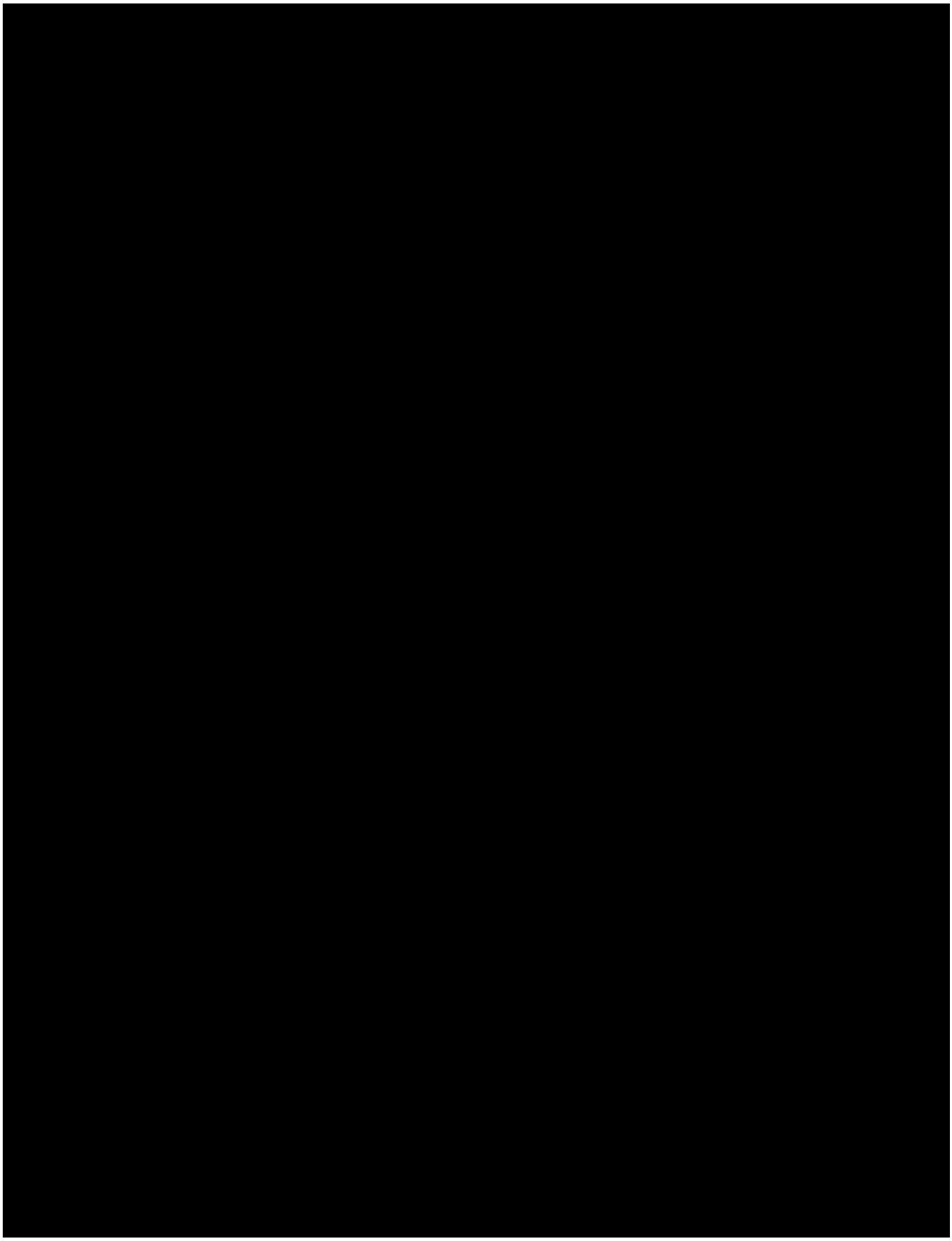
All safety and efficacy analyses will be integrated analyses that include data from all the preceding pivotal studies (MT10109L-001, -002, -005, and -006) and the extension study (MT10109L-004). Participants can receive up to 3 interventions in the lead-in studies. Data from up to 3 treatment cycles in the preceding studies and data from the treatment cycles in the -004 extension study will be analyzed as outlined in this analysis plan. All participants enrolled in Study MT10109L-004 will be included for analysis, whether they receive study intervention or not. Specifications of tables, figures, and data listings are contained in a separate document.

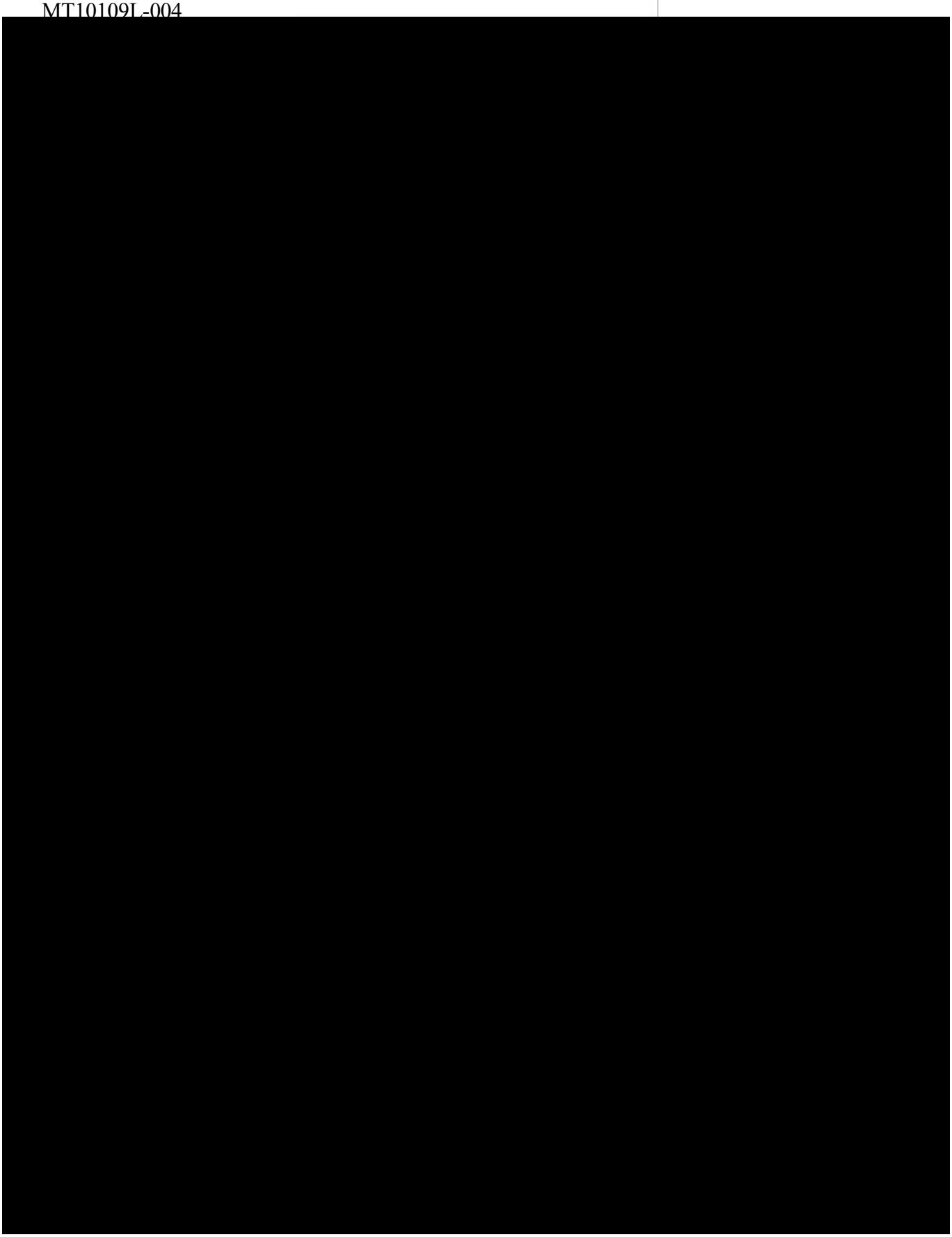
1.1. Objectives and Endpoints

Table 1-1 Objectives and Endpoints

Objective Clinical Category	***Statistical Category***	***Estimand/Variable***
Primary Objective: *To evaluate the long-term safety of repeat treatments of MT10109L in participants with* moderate to severe *GL, LCL, or both GL and LCL*		
Safety: Incidence of adverse events	*Primary*	• *Variable: Presence of TEAEs* • *Population: ITT* • *Analysis: Categorical descriptive* • *Number and percentage of participants in individual categories* ○ *Participants with ≥ 1qualifying event counted once per individual category*
Safety: Vital signs	*Primary*	• *Variable: Change from baseline in vital signs at each cycle after intervention and end of study* • *Population: ITT* • *Analysis: Continuous descriptive for baseline, postbaseline, and change from baseline values* *N1 = participants with nonmissing values at both baseline and the specified postbaseline analysis visit/timepoint*
Safety: Binding and neutralizing antibodies	*Primary*	• *Presence of binding and neutralizing antibodies* • *Population: ITT* • *Analysis: Categorical descriptive*







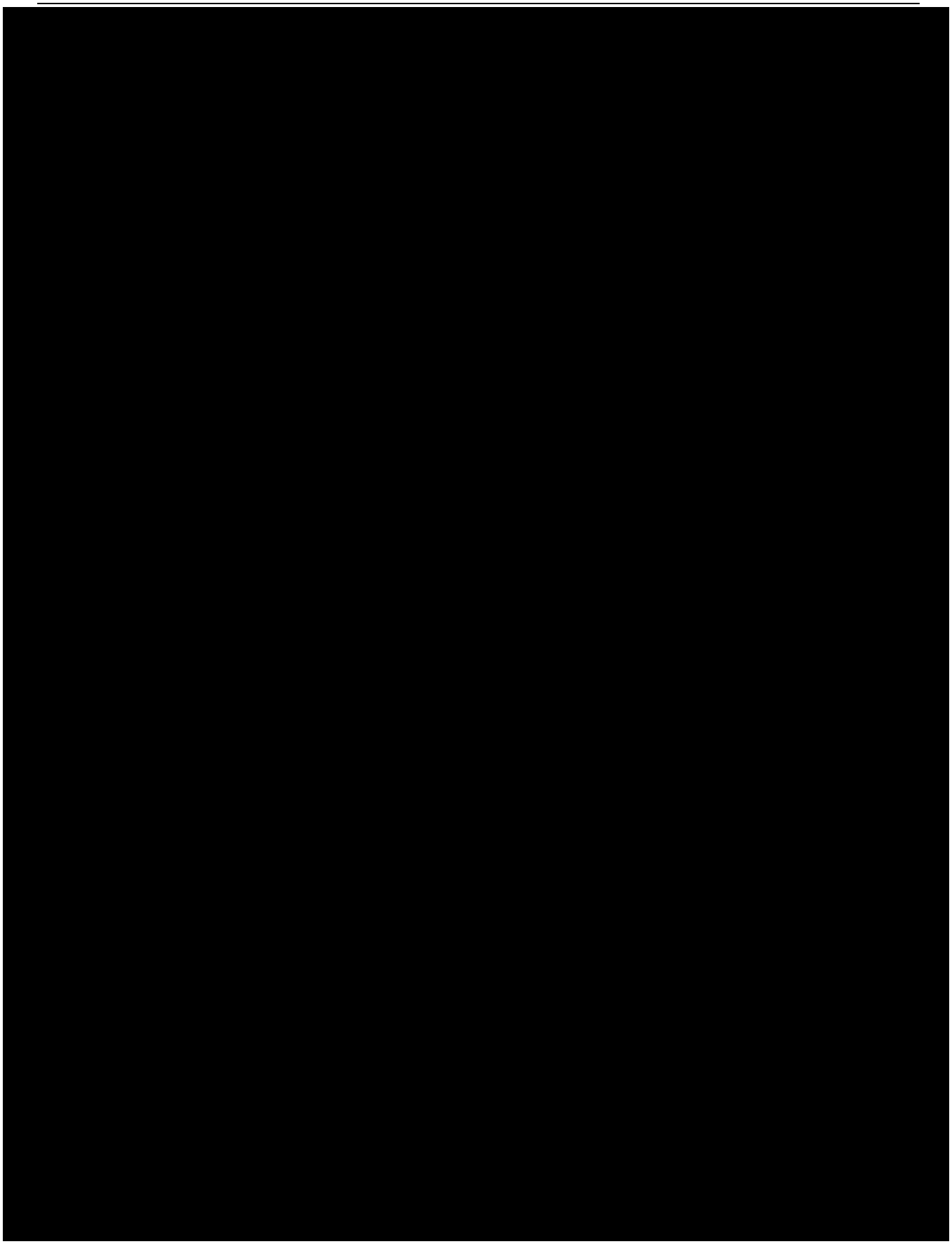
1.2. Study Design

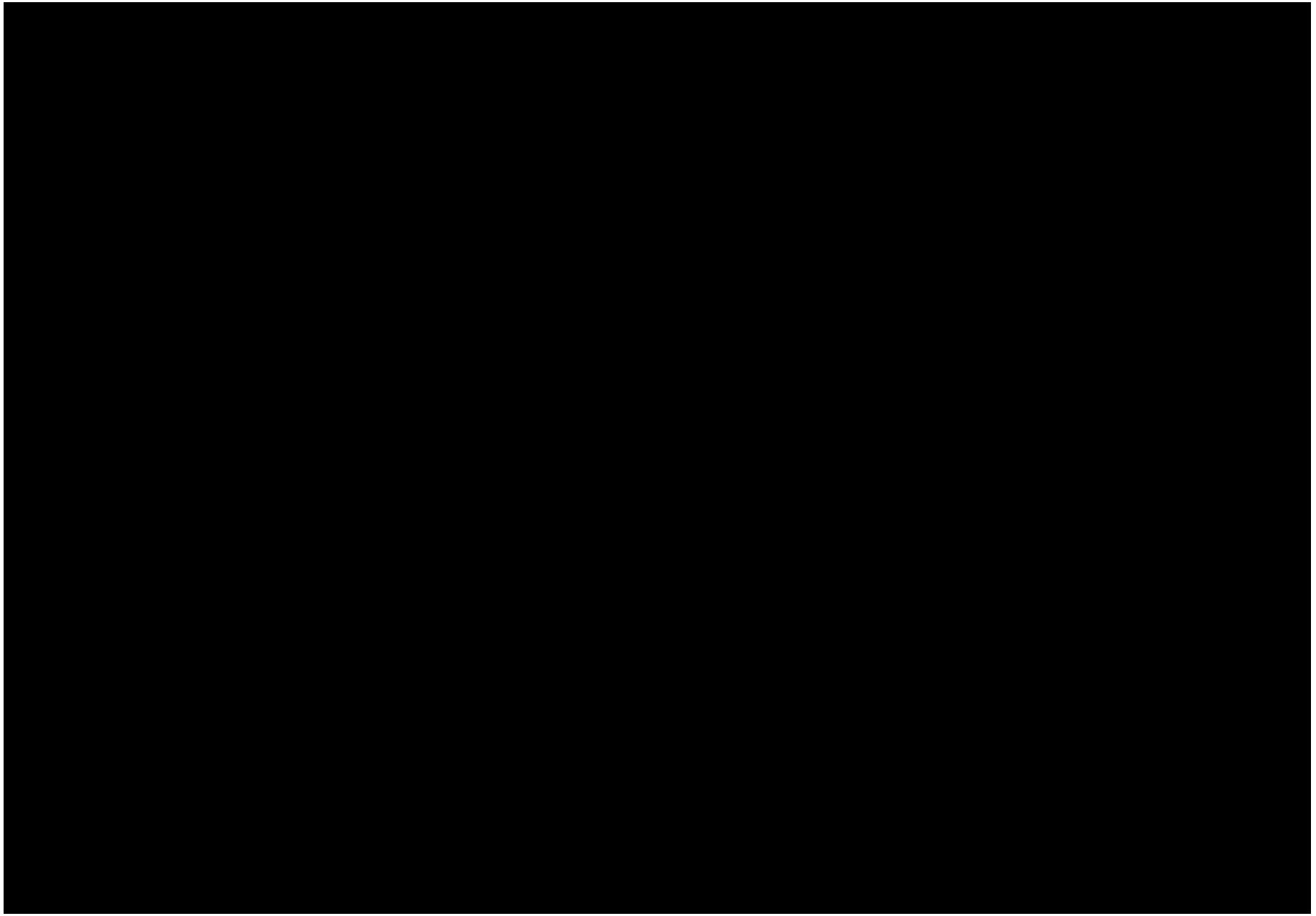
Overall Study Design:

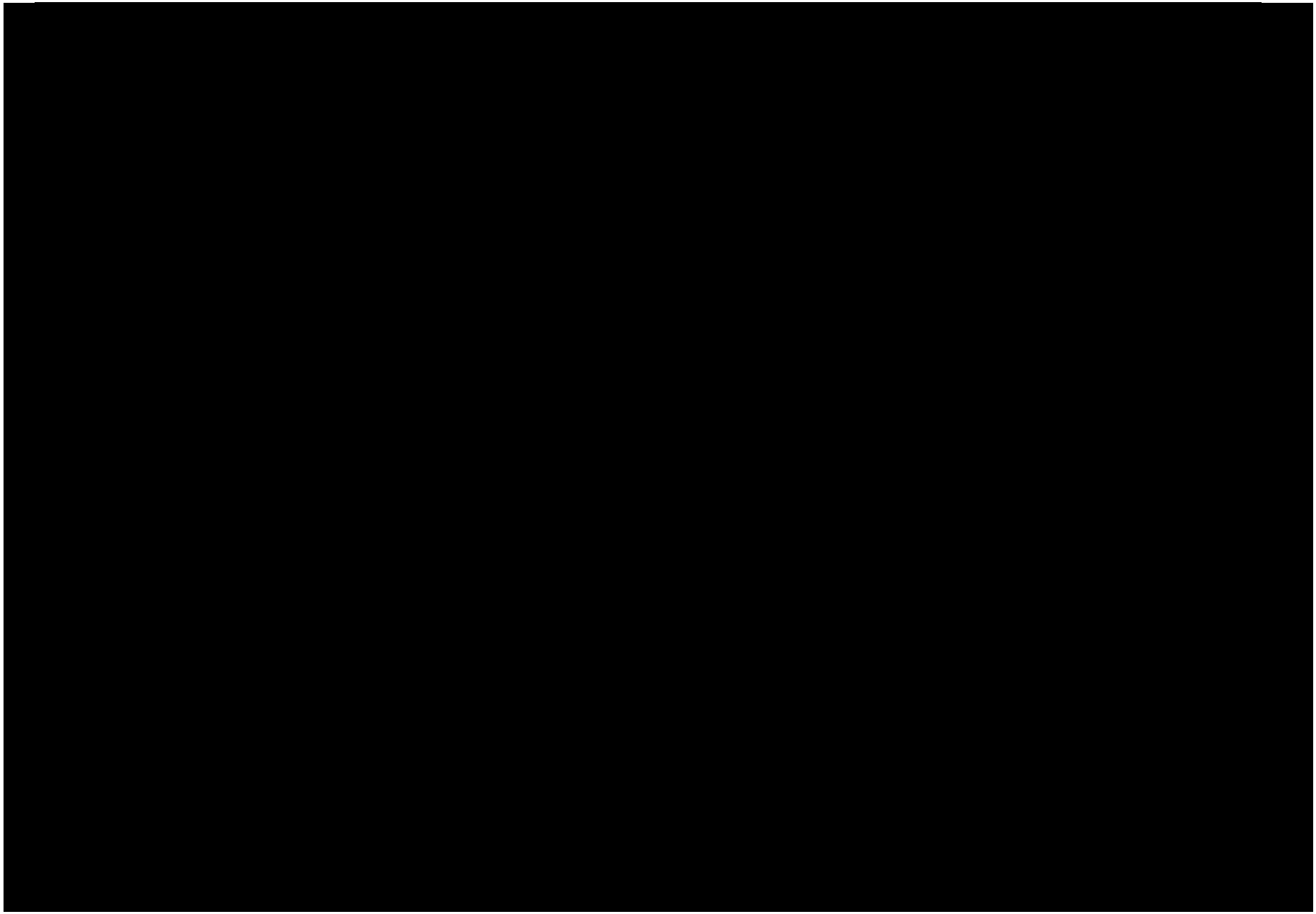
- Global, multicenter, open-label, repeat treatment, parallel-group
- Treatment Group: MT10109L [redacted] administered in the same treatment area(s) with the same number of injections and injection sites as in their lead-in Phase 3 study.
- Study Duration: 24-month treatment period
- Participants ≥ 19 years old who completed Studies MT10109L-001 (GL), MT10109L-002 (LCL), MT10109L-005 (GL with or without LCL), and MT10109L-006 (LCL with or without GL) and meet study entry criteria may receive up to 9 study interventions in Study MT10109L-004
- Approximately 800 participants will be enrolled at approximately 44 global sites [redacted]
- Based on meeting retreatment criteria for each intervention, the first intervention in this study may occur at the Day 1 visit and the last intervention may occur at the Day 690 visit (30 days prior to Day 720/study exit).
- [redacted]
- Participants who complete this study will have an exit visit on Day 720.

[redacted]

[redacted]







[redacted]

[redacted]

- Adverse events (AEs) will be monitored in-clinic for ≥ 30 minutes after each study intervention, [redacted] at each subsequent scheduled in-clinic or telephone visit, and at any other time an AE is reported.
- [redacted]

2. Sample Size Determination

For this long-term follow-up study, no formal statistical power/sample size calculation was used. Approximately 800 participants are anticipated to be rolled-over into this study. This number is estimated from the sample size from the lead-in Phase 3 studies (MT10109L-001, -002, -005, and -006);

3. Statistical Hypotheses

Not applicable.

4. Populations for Analysis

The analysis populations will consist of participants as defined below:

Table 4-1 Analysis Populations

Population	Definition	Study Treatment by Cycle	Lead-in and Extension Study Possible Treatment Regimens
Intent-to-Treat (ITT)	All participants who enrolled in Study MT10109L-004 and received at least 1 intervention (MT10109L or placebo) in their prior Phase 3 study (MT10109L-001, -002, -005, or -006) or in the current study. Participant data from the current study will be integrated with the corresponding participant data in Studies MT10109L-001, -002, -005, and -006. [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

5. Statistical Analyses

5.1. General Considerations

[redacted].

The proportions of participants who achieve the efficacy endpoints will be summarized with frequency tables. The 95% CI for responders will be estimated based on the observed data by intervention group and by treatment cycle. For the US FDA, efficacy analyses will be based on the ITT population.[redacted]

The safety analyses will be based on the ITT population.

Statistical analyses will be performed using version 9.4 (or newer) of statistical analysis software (SAS) on a Linux operating system.

[redacted]

[redacted]

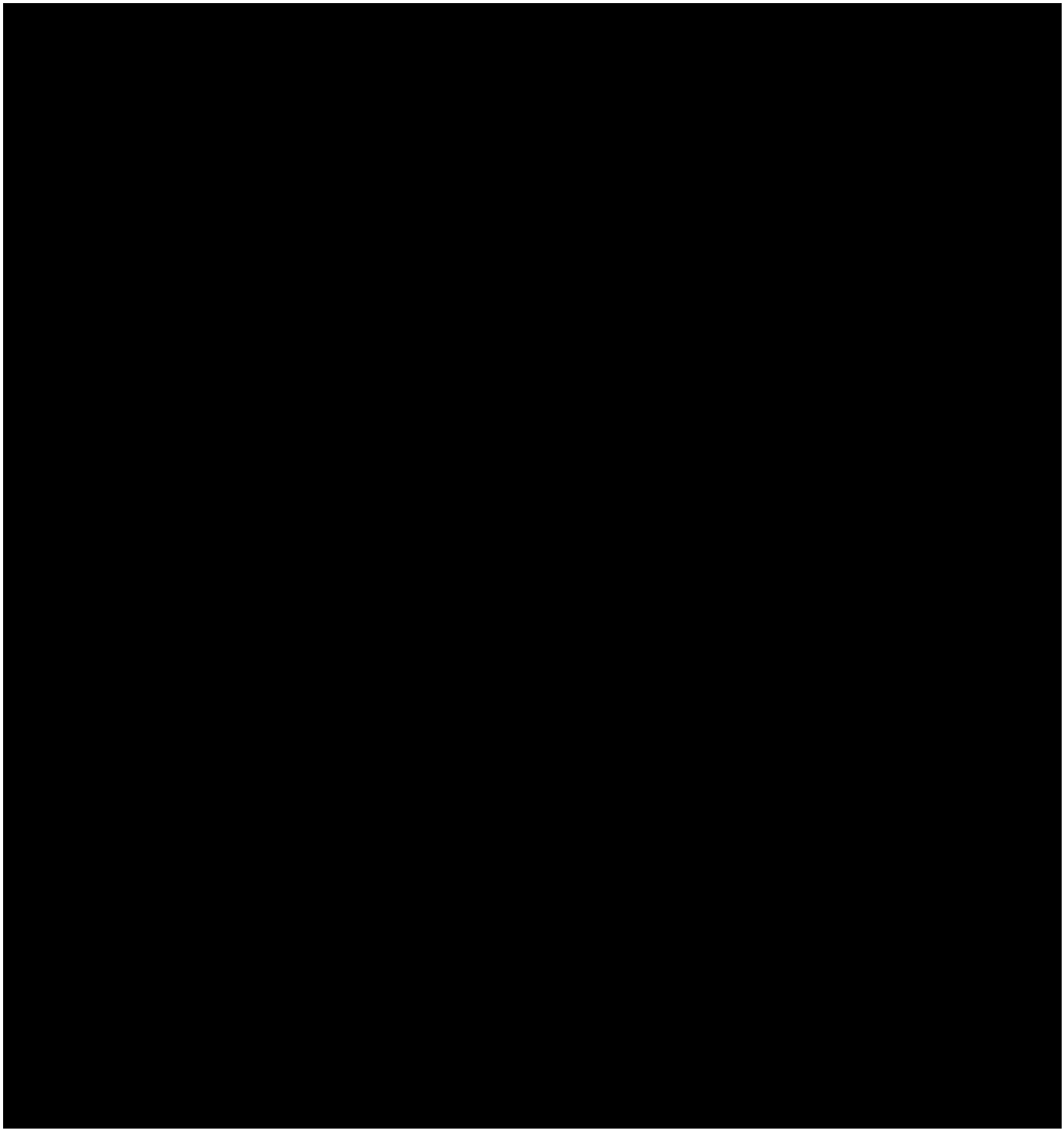
5.1.1. Treatment Group and Treatment Cycles

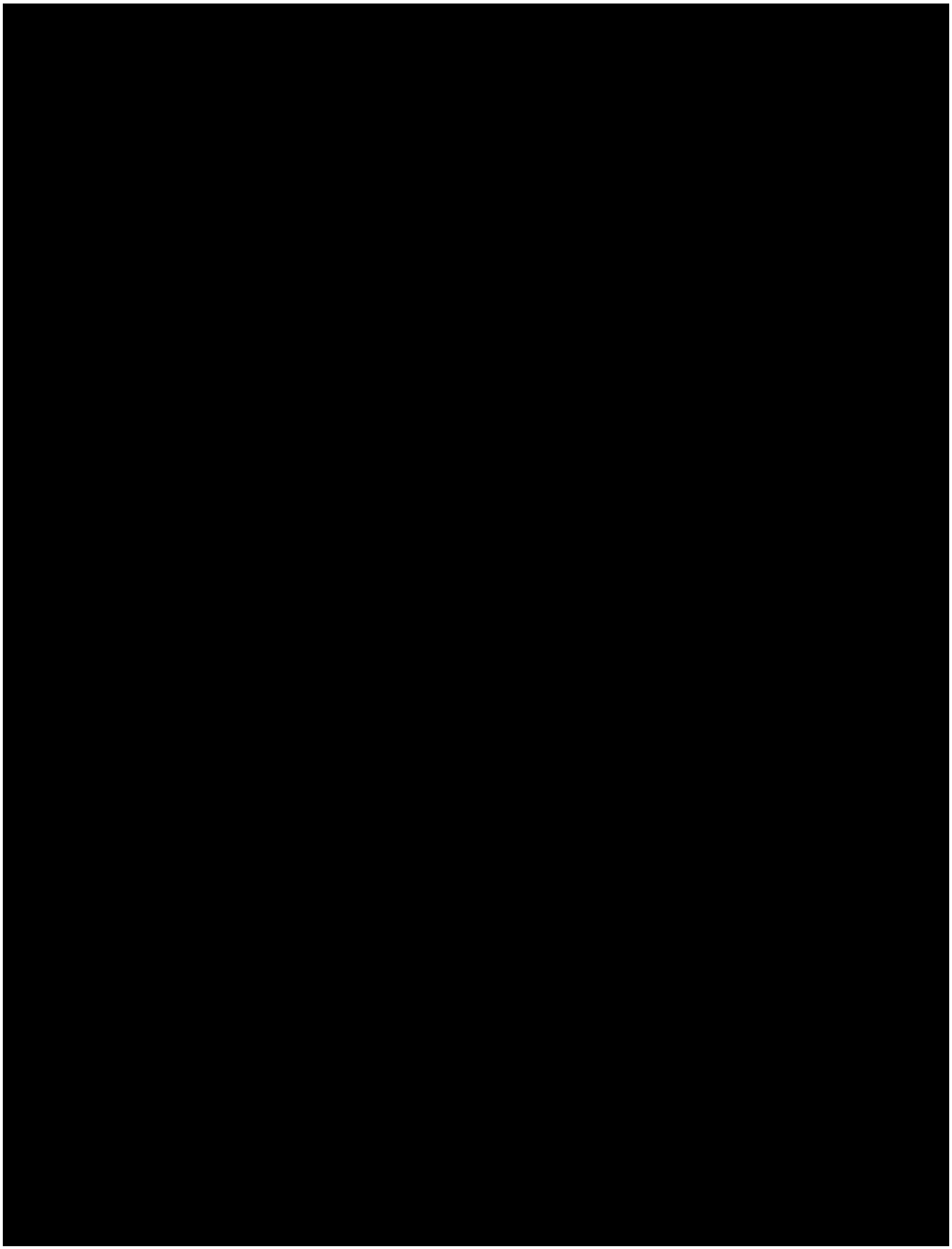
All safety and efficacy analyses will be integrated analyses that include data from both the lead-in studies and the MT10109L-004 extension study, for participants enrolled into the extension study.

A study treatment cycle is considered to start on the day of treatment with study intervention and end on the day prior to the next study intervention or on the study exit day if there are no subsequent interventions. The nomenclature used will be “treatment cycle 1”, “treatment cycle 2”, “treatment cycle 3”, “treatment cycle 4”, “treatment cycle 5”, “treatment cycle 6”, “treatment cycle 7”, “treatment cycle 8”, “treatment cycle 9”, “treatment cycle 10”, “treatment cycle 11”, and “treatment cycle 12” for the lead-in and extension study possible treatment regimen cycles.

[redacted]

Demographic and baseline characteristic, disposition, treatment-emergent adverse event (TEAE) for entire study, vital signs, and immunogenicity tables will be summarized under lead-in and extension study possible treatment regimens specified in Table 5-3 . It will use planned treatment in lead-in study/ planned treatment in extension study for lead-in and extension study possible treatment regimens.





[redacted]

In general, there will be no substitution of missing time or date. However, any partial information will be utilized to its full extent wherever sensible. For example, a medication may be classified as a prestudy medication if the partial information of the medication ending date with only month and year permits a determination that the medication ended prior to the injection date of the study intervention.

5.1.4. Descriptive Statistics

Data will be summarized with descriptive statistics and/or response frequencies. Descriptive statistics for continuous variables include the sample size (N), mean, standard deviation (SD), median, minimum (Min), and maximum (Max). Descriptive statistics for categorical variables include the sample size (N) and frequency (counts and percentages).

5.1.5. Significance Level and Confidence Intervals

The level of significance used for all statistical tests will be 0.05, 2-sided, unless stated otherwise.

For all endpoints for which confidence intervals are calculated, the following methods of calculation apply, unless otherwise stated.

For dichotomous variables, 2-sided 95% confidence intervals for proportions will be calculated based on the normal distribution approximation.

5.1.6. Dictionaries

The Medical Dictionary for Regulatory Activities (MedDRA Version 24.1) will be used to code AEs, medical history, and procedures. MedDRA primary system organ class (SOC), MedDRA high level term (HLT), together with the drug record number and base preferred drug name from the enhanced version of World Health Organization Drug Dictionary (WHO DDE) Global March 2021, will be used to classify all medications (ie, prior or concomitant) recorded in the study. Base preferred name is the WHO DDE drug preferred name assigned to the 11-digit code of drug record number+01+001.

5.1.7. Units

Metric system units will be used; degrees Celsius for temperature, kilograms (kg) for body weight, and centimeters (cm) for height.

5.1.8. Investigator Sites

The site number for Studies MT10109L-001, -002, -005, or -006 will be used for all tables and listings.

5.1.9. Study Intervention

If "Was the subject injected per protocol?" ticked as yes, the dose used of each injection will follow per protocol section 6.1.2 in extension period.

5.2. Participant Dispositions

5.2.1. Disposition and Exit Status

The analysis will be performed using the ITT [redacted] populations for overall study and by treatment cycle. The lead-in and extension study possible treatment regimens will be used.

The disposition of study participants consists of a summary of the number of participants enrolled and available in the ITT [redacted] populations by treatment regimen and overall. [redacted]

Tabulation of the numbers and percentages of participants in each exit status category (ie, AE, pregnancy, lost to follow-up, lack of efficacy, withdrawal by subject, physician decision, death, progressive disease, protocol deviation, noncompliance with study drug, study terminated by sponsor, site terminated by sponsor and other) will be provided for each treatment regimen of each treatment cycle. Discontinued participants will be listed along with the corresponding reason(s) for early withdrawal from the study.

5.3. Primary Endpoints Analysis

The primary endpoints are incidence of AEs, change from baseline in vital sign parameters, and presence of binding and neutralizing antibodies for safety.

5.3.1. Definition of Endpoints

5.3.1.1. Adverse Events

An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.

[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.

An AE will be considered a treatment-emergent serious adverse event (TESAE) if it is a TEAE that additionally meets any serious adverse event (SAE) criteria.

A SAE is defined as any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. All cancer AEs are considered SAEs by Allergan. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs.

5.3.1.2. Vital Signs

Vital sign measurements are pulse rate (beats per minute), respiration rate (breaths per minute), and blood pressure (mm Hg). Participants are to be seated for at least 2 minutes before measurements are collected [redacted]

5.3.1.3. Immunogenicity Analyses

Blood samples for immunogenicity testing will be collected from each participant [redacted]

5.3.2. Main Analytical Approach

5.3.2.1. Adverse Events

Adverse events will be coded from the verbatim text into preferred term (PT) and SOC by using the MedDRA dictionary. [redacted]

[redacted]

For an ongoing AE from the preceding Studies MT10109L-001, -002, -005 and -006 to extension Study MT10109L-004, the onset date, PT, and onset severity will be used to match the same ongoing AE from different studies.

The incidence of AEs will be summarized with frequencies (counts and percentages) by treatment regimen for all events regardless of causality, for all SAEs regardless of causality, and for treatment-related AEs (those with a reasonable possibility of being caused by the study intervention in the investigator's opinion).

The incidence of AEs for all, SAEs (see Section 5.3.1 for definition), and treatment-related AEs will be presented and summarized by MT10109L cycle and over the entire study as follows unless otherwise specified:

1. Overall incidence of TEAEs:

This summary will include the incidence of all TEAEs, the incidence of TEAEs related to treatment, the incidence of TESAEs, the incidence of TESAEs related to treatment, the incidence of TESAEs not-related to treatment, AEs that lead to study discontinuation, and death.

2. By PT within primary SOC:

This summary will present the incidence of each PT within the primary SOC, as well as the overall primary SOC incidence. Primary SOCs will appear alphabetically, and PTs within each SOC will be sorted by descending incidence. A participant with multiple events coding to the same PT within a primary SOC will be counted only once for the PT within that primary SOC.

3. By maximum severity of PT within primary SOC:

For all TEAEs, a summary will present the incidence of the maximum severity of each PT within a primary SOC for the entire study only. Primary SOCs will appear alphabetically, and PTs within each SOC will be sorted by descending incidence. For a given AE, if more than one severity grade is reported for a given participant, the worse severity grade will be included in the tabulation. If a participant has multiple events coding to the same PT within a primary SOC, the maximum severity for that participant will be used, and that participant will be counted only once for that PT within that primary SOC. This summary will be presented and summarized by MT10109L cycle only.

4. TEAEs leading to discontinuation by PT within primary SOC:

This summary will present the incidence of each PT within the primary SOC, as well as the overall primary SOC incidence for AEs leading to premature discontinuation from the study.

All AEs will be presented in a by-subject listing, detailing the lead-in/extension treatment, first treatment date, treatment cycle of AE, treatment date for corresponding treatment cycle, verbatim term, the preferred term (PT), system organ class (SOC), location of event, start date/day (number of days since Studies MT10109L-001, -002, -005, and -006 Day 1), end date/day (number of days since Studies MT10109L-001, -002, -005, and -006 Day 1), TEAE or not, severity, outcome, relationship to study treatment, relationship to study procedure, [redacted], action taken to study treatment, action taken to study procedure, serious adverse event criteria and leading to discontinuation.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.3.2.2. Vital Signs

Descriptive summaries (n, mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for vital signs (systolic and diastolic blood pressure, pulse, and respiration rate). These summaries will be presented by study intervention for each intervention and by visit.

5.3.2.3. Immunogenicity Analyses

A 2-stage assay approach will be used for the detection of binding antibodies against MT10109L and neutralizing antibodies against MT10109L in participants' serum. In Stage 1, serum samples will be screened for the presence of binding antibodies using the validated enzyme-linked immunosorbent assay (ELISA) in a 3-tier format (screening, confirmation, and titering). The screen positive serum samples will be subsequently immunodepleted to confirm that the binding antibodies are specific to MT10109L and titered to assess the extent of antibodies present. In Stage 2, only samples testing positive in the antidrug antibody (ADA) confirmatory assay will be evaluated in the mouse protection assay (MPA).

[redacted]

5.4. Other Safety Analyses

5.4.1. Extent of Exposure

Participants' exposure to the study intervention will be summarized by duration of treatment exposure, number of treatment cycles, and treatment cycle interval duration.

Duration of treatment exposure will be calculated for each extension treatment regimen [redacted] based on the number of days between the date of the first injection of that treatment (F) and the date of study exit in the extension study (E). The actual calculation used will be E – F + 1. If the date of study exit is missing, the date of the last visit will be used. [redacted]

Participants' exposure to study intervention will be summarized by total duration of treatment exposure [redacted] In addition, for the entire study, the number and percentage of participants receiving 1, 2, 3 up to 12 study interventions will be summarized.

5.4.1.1. Treatment Compliance

Participants will receive all doses under the direct supervision of study site personnel. Study intervention compliance will not be calculated.

The study site will keep an accurate drug disposition record that specifies the amount of study intervention administered to each participant and the date of administration.

5.4.2. Additional Safety Assessments

No laboratory or electrocardiogram (ECG) data will be collected for this study.

Urine pregnancy tests are performed prior to each treatment and at exit visit for females of childbearing potential. Participants with positive pregnancy test results will be listed by treatment regimen, including urine sample collection date, days since Day 1 treatment (of Studies MT10109L-001, -002, -005, or -006) and days since most recent treatment.

[redacted]

5.5. Other Efficacy Analyses

For US FDA, the efficacy analyses will be based on the ITT population. [redacted]

Continuous descriptive statistics include: N1 (number of participants with nonmissing values at both baseline and the specified postbaseline analysis visit), mean, SD, median, minimum, and maximum.

Categorical variables will be summarized by number and percentage of participants. The proportions of participants who achieve the efficacy endpoints will be summarized with frequency tables. The 95% confidence interval for responders will be estimated based on the observed data by intervention group and by intervention cycle.

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
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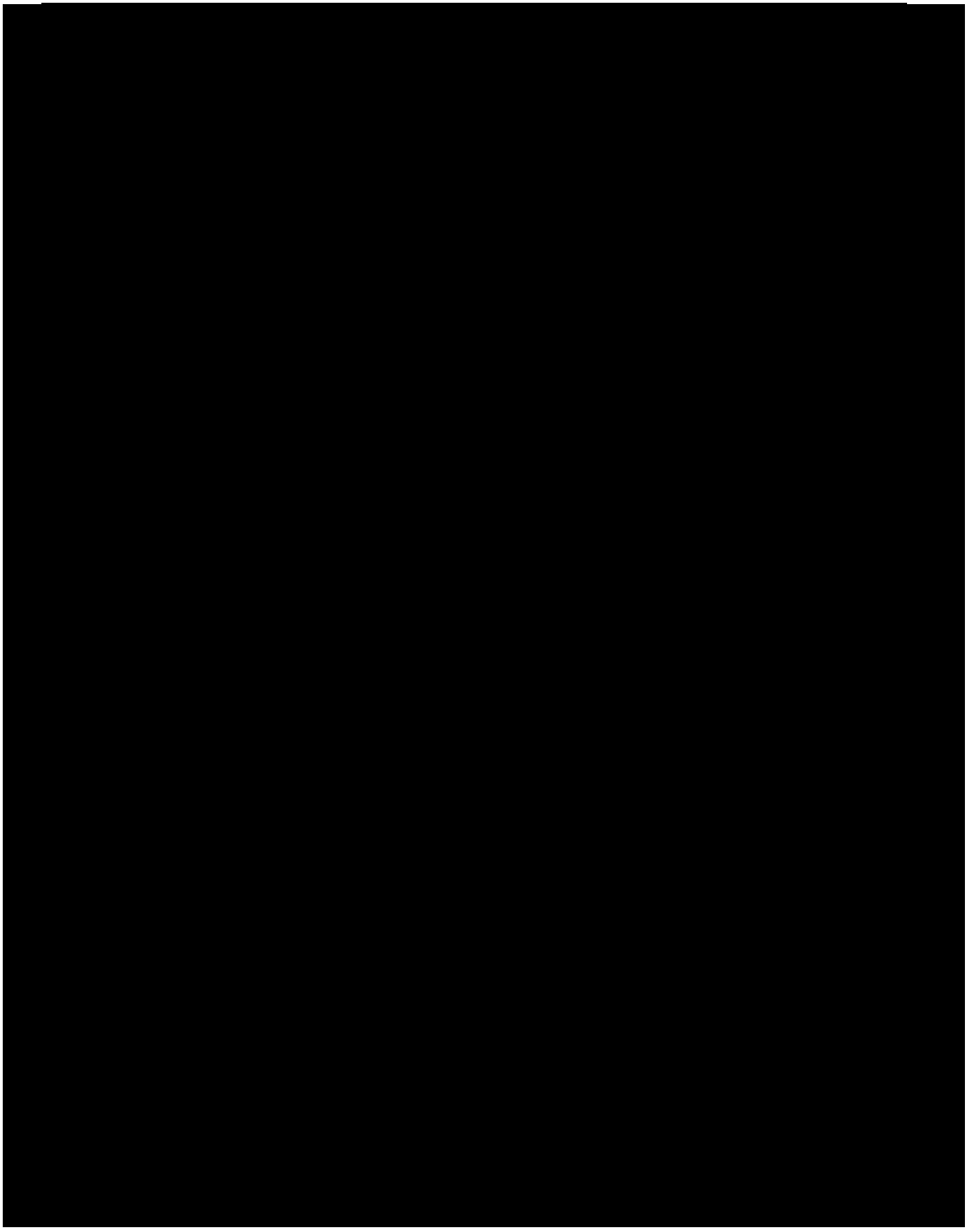
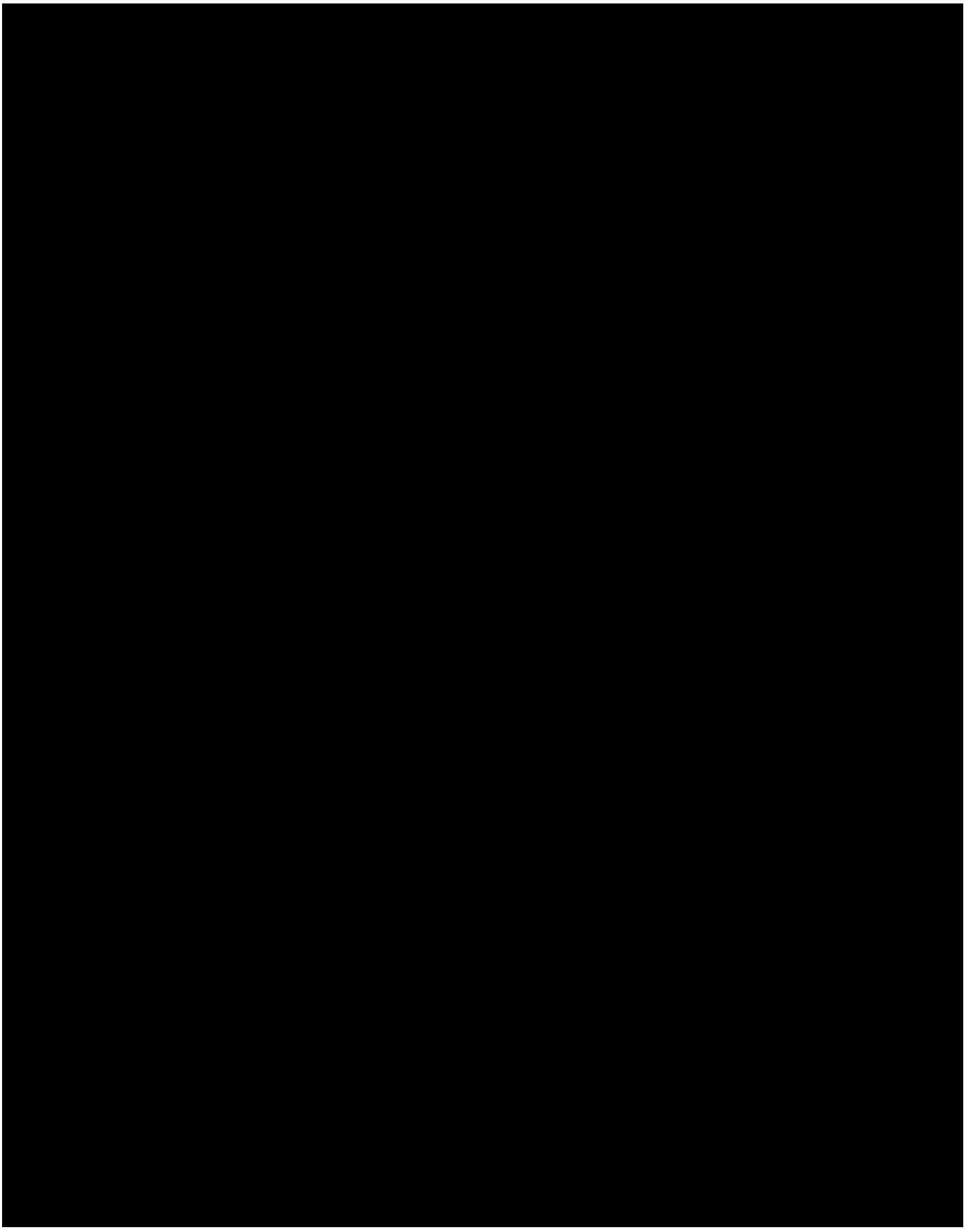
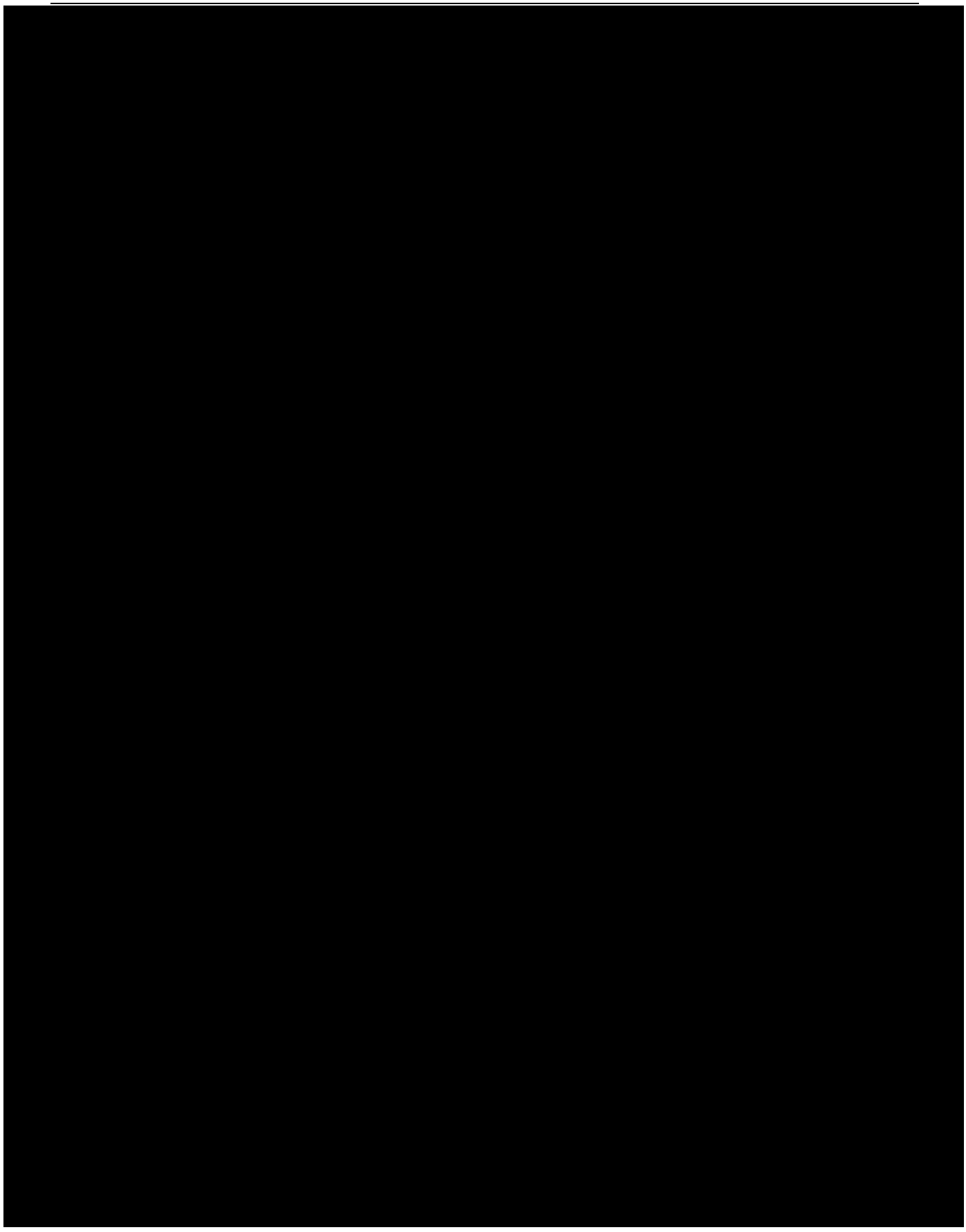


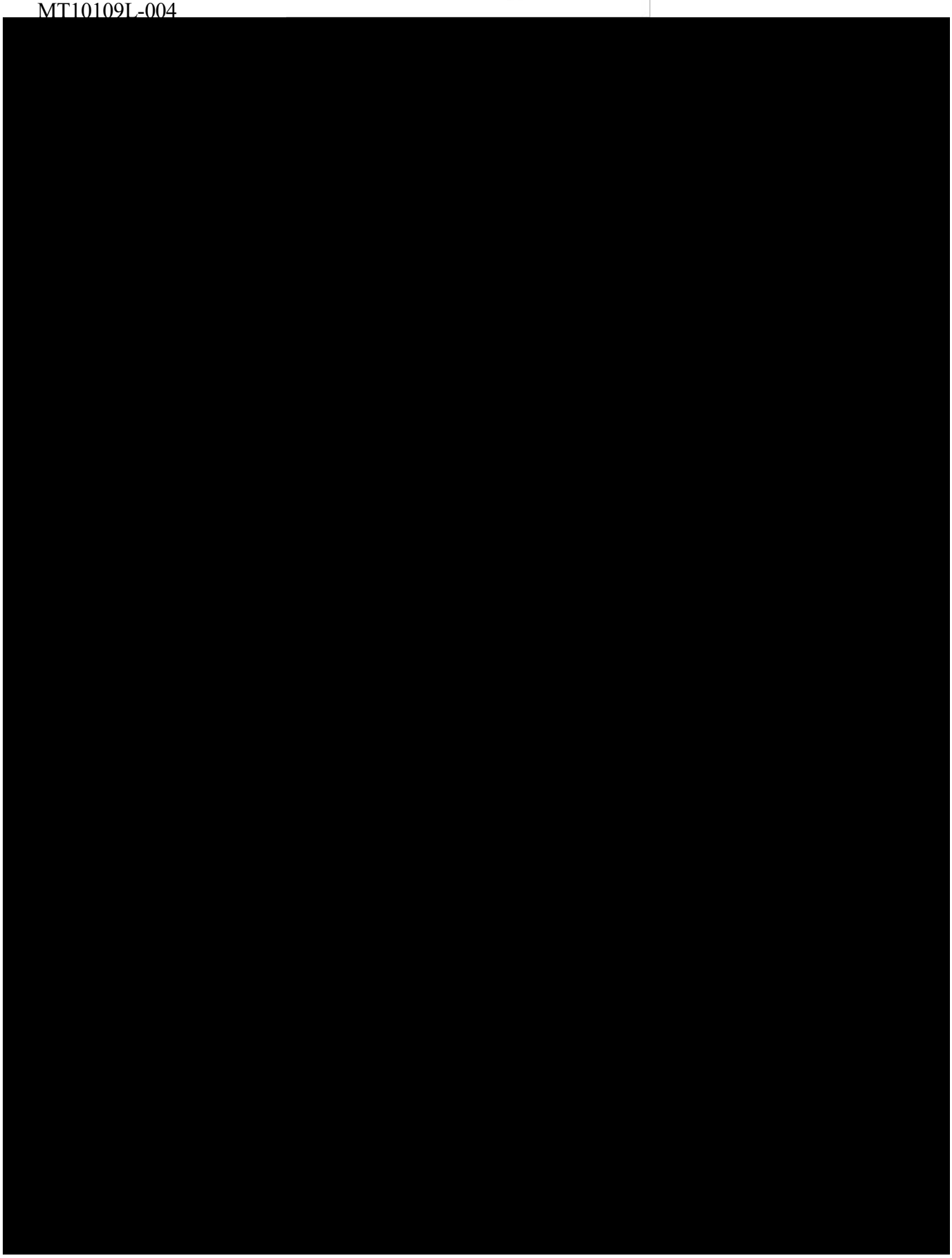




6. Supporting Documentation

6.1. Appendix 1 List of Abbreviations

AE	adverse event
BMI	Body mass index
BoNT/A	botulinum toxin type A
DB	double blind
ECG	electrocardiogram, electrocardiographic
EU	European Union
ELISA	enzyme-linked immunosorbent assay
US FDA	United States food and drug administration
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
GL	glabellar lines
HLT	high level term
ITT	intent to treat
LCL	lateral canthal lines (also called crow's feet lines/CFL)
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MT10109L	NivobotulinumtoxinA
OL	open-label
[redacted]	[redacted]
PRO	patient reported outcome
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
WHO DDE	world health organization drug dictionary enhanced



6.3. Appendix 3: Supporting Study Information

6.3.1. Demographics

The analysis and summary of all demographic and other baseline characteristics will be performed using the ITT [redacted] population unless otherwise specified. The lead-in and extension study possible treatment regimens will be used unless otherwise specified. Demographic data will be collected at the Studies MT10109L-001, - 002, -005, and -006 screening visit, including age, gender, race, weight, height, and Body Mass Index (BMI). Age, weight, height, and BMI will be analyzed with the descriptive statistics (sample size, mean, SD, median, Min, and Max) by lead-in and extension study possible treatment regimens. Age group, gender, and race will be analyzed with frequency (counts and percentages) by lead-in and extension study possible treatment regimens. Age will be classified into 2 age groups: < 65 and ≥ 65. Race will be classified as Caucasian and non-Caucasian.

The algorithm for calculating age in years will be as follows:

> If the participant's birthday has been reached in the baseline (Day 1) year, age = year of baseline minus year of birth
>
> If the participant's birthday has not yet been reached in the baseline (Day 1) year, age = year of baseline minus year of birth -1

[redacted]

6.3.2. Baseline and Disease Characteristics

For the ITT population, the distribution of the baseline severity of GL and LCL at maximum contraction and at rest will be summarized for each area separately for the FWS assessments by lead-in and extension study possible treatment regimens.

[redacted].

6.3.3. Protocol Deviations

Unique participants reporting significant protocol deviations will be summarized in total and by intervention group for the ITT population.

A listing of any significant protocol deviations will be provided.

6.3.4. Medical History

Medical history includes all medical conditions that the participant had in the past or currently have prior to injection on the Day 1 visit of Studies MT10109L-001, -002, -005, and -006. The frequency (numbers and percentages) of participants reporting each medical history will be

tabulated by lead-in and extension study possible treatment regimens for the ITT population by MedDRA primary SOC in descending order.

6.3.5. Prior/Concomitant/Follow-up Medications/Procedures

Prior and concomitant medications/procedures will be tabulated by lead-in and extension study possible treatment regimens for the ITT population.

6.3.5.1. Prior and Concomitant Medications

Prior medications include all medications prior to the Day 1 Baseline Visit of Studies MT10109L-001, -002, -005, and -006, whether or not the medication is continuing beyond the Baseline Visit. Concomitant medications encompass all medicinal products that the participant was taking prior to the Studies MT10109L-001, -002, -005, and -006 Day 1 Baseline Visit that are ongoing at the visit, in addition to all medications that have a start date on or after the Day 1 visit date.

Handling of partial and missing date in CM for the determination of prior versus concomitant medication is described in section 6.4.6

Concomitant medications will be summarized by treatment, WHO-DD Anatomical-Therapeutic-Chemical (ATC) classification and PT, displaying counts and percentages of subjects who reported using at least one medication. All prior and concomitant medications will also be presented in a by-subject listing.

Prior and Concomitant ProceduresPrior procedure (with stop dates prior to first injection of MT10109L), and concomitant procedure (ongoing or medications with a start date after first injection of MT10109L). The frequency (number and percentages) of participants who have undergone each procedure will be tabulated for each lead-in and extension study possible treatment regimens by MedDRA SOC and PT.

The tables will display counts and percentages of subjects who reported at least one procedure in each SOC and PT. At each level of summarization, a subject reporting more than one event will be counted only once using. All prior and concomitant procedure will be presented in a by-subject listing, detailing the verbatim term, PT, SOC, start date and indication.

[redacted]

6.4. Data Handling Convention

6.4.1. Analysis Window

For analyses by visit, the following visit windows will be used to determine visit assignment, based on the observed number of days relative to the start of each treatment cycle (the day of the injection) (Table 6-1).

If two or more values fall within the same analysis window, the one closest to the target date will be used.

6.4.2. 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 non-missing 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 non-missing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics.

6.4.3. 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.

6.4.4. 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.

6.4.5. Missing Date Information for Adverse Events

Partial AE 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 intervention, yet the corresponding AE was not observed pretreatment, then impute the onset date as the first treatment date. Imputed partial AE onset date will only be used to determine the AE onset cycle.

Other partial AE dates will not be imputed. All partial dates will be listed “as is” in the data listings. If both AE onset date and first injection of MT10109L date’s time are recorded, datetime will be used for imputation in lead in study.

6.4.6. Missing Date Information for Medications

There will be no imputation for missing or partial start/end date for medication. Partial dates entered in the prior and CM form will be imputed for the purposes of determining whether the record is a concomitant or prior medication in analysis flag based on the following: 1) Medications that are not ongoing and have a medication stop date with a missing day and non-missing month will be assumed to occur on the last day of the non-missing month. 2) Medications that are not ongoing and have a medication stop date with missing day and month will be assumed to occur on the last day of the non-missing year (i.e., December 31).

7. References

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