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Study ID: 191622-120

Title: BOTOX® in the Treatment of Urinary Incontinence Due to Neurogenic Detrusor Overactivity in Patients 5 to 17 Years of Age

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Allergan
Biostatistics
Analysis Plan – Clinical Study Report

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1. Introduction

This document details the planned analysis for Study 191622-120. This study is a multicenter, randomized, double-blind, parallel group study to evaluate the safety and efficacy of BOTOX for the treatment of urinary incontinence due to neurogenic detrusor overactivity (NDO) in patients 5 to 17 years of age who have not been adequately managed with anticholinergic therapy.

There will only be one analysis for this study. When all patients in Study 191622-120 exit the study there will a database lock (DBL) and a clinical study report (CSR) will be generated. This analysis plan outlines the outputs to be included in the CSR.

1.1 Primary Study Objectives and Design

The primary objective of this study is to evaluate the safety and efficacy of BOTOX for the treatment of urinary incontinence due to NDO in patients 5 to 17 years of age who have not been adequately managed with anticholinergic therapy. Patients in this study are randomized to 1 of 3 treatment groups in a 1:1:1 ratio:

- 50 units (U) BOTOX (not to exceed 6 U/kg)
- 100 U BOTOX (not to exceed 6 U/kg)
- 200 U BOTOX (not to exceed 6 U/kg)

In order to ensure that the upper dosing limit of 6 U/kg is not exceeded, the actual dose administered is adjusted based on patient weight, if necessary.

Patients will be evaluated during a screening period for eligibility. Eligible patients will be randomized and receive treatment/injection on Day 1. Patients are centrally randomized. In order to ensure balance across treatment groups, patients are stratified by age (< 12 years or ≥ 12 years), and baseline daytime urinary incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day diary collection period).

Patients will participate in the study until one of the following exit criteria is met, whichever occurs first:

- patient has qualified for retreatment (retreatment to occur in the extension study 191622-121, for patients who elect and qualify to enroll),
- patient has completed 48 weeks after treatment (BOTOX injection), if qualification for retreatment does not occur (i.e., completes the 48 week visit), or
- patient prematurely discontinues the study

In this study, patients are evaluated at scheduled visits at 2, 6, and 12 weeks after treatment/injection (week 2, 6 and 12 visits). After the week 12 visit, there are alternating telephone and clinic visits every 6 weeks until the patient exits the study. Patients will exit the study once they qualify for retreatment. The visit where the patient qualifies for retreatment will also become the exit visit. Alternatively, if qualification for retreatment does not occur, patients will exit the study 48 weeks after study drug injection.

The primary efficacy measure is daytime urinary incontinence episodes, and the primary time point is week 6.

1.2 Secondary and Other Objectives

Not applicable.

1.3 Sample Size

The sample size calculation for this study is determined empirically. Sample size assessment is presented in Section 7.7 of the study protocol.

1.4 Experimental Unit and Analysis Unit

The experimental unit is study subject. The primary efficacy assessment is daytime urinary incontinence episode measured at the patient level.

2. Analysis Populations and Data Conventions

2.1 Analysis Populations

Patients in this study are randomized to one of three treatment groups, namely, 50, 100 or 200 U BOTOX treatment groups. Within each randomization group, the dose that is actually received by a patient can vary due to the dose limit of 6 U/kg (i.e., the dose is adjusted based on the patient's weight). Table 1 presents the BOTOX treatment arms to be used for analysis, if different than randomized.

Table 1 BOTOX Treatment Groups Based on Actual Dose Administered

Actual Dose Administered	BOTOX Treatment Group
< 75 U	50 U BOTOX
75 U ≥ and < 150 U	100 U BOTOX
≥ 150 U	200 U BOTOX

In order to maintain blinding of the BOTOX dose received, the drug is reconstituted by an independent drug reconstitutor (IDR) based on randomization assigned by IVRS/IWRS (which also includes the patient's weight as provided in IVRS/IWRS). Study drug accountability and reconstitution records are then reviewed and confirmed by independent drug monitors (IDM). If an incorrect dose was administered, the IDM will complete the "Incorrect Unit Dose Administered" form and the "incorrect unit dose administered" will be entered into the electronic case report form (eCRF).

Patients will be assigned to actual treatment groups for analysis purposes as follows:

1. If the "incorrect unit dose administered" is populated in the eCRF, this dose will be used and adjusted per Table 1 above.

2. If the "incorrect unit dose administered" is not populated in the eCRF, then the randomized dose (ie, 50U, 100U, or 200U) and the patient's weight recorded in IVRS/IWRS at the time of randomization will be utilized to determine the actual dose administered as described in section 12.1 of the study protocol. The dose administered will then be adjusted per Table 1 above.

Two populations will be used in the statistical analysis of this study: modified intent-to-treat (mITT) and safety.

The analysis of demographics, baseline characteristics and efficacy will be based on the mITT population while the safety population will be used for all safety analysis.

Modified Intent-to-Treat (mITT) Population

The mITT population will include all randomized patients who received BOTOX injection on Day 1 (randomization day and date of injection). Patients in the mITT population will be analyzed on an as-randomized basis, except for patients who received less than their randomized dose due to the patient's weight and the dose limit of 6 U/kg (as per the protocol). Such patients will be grouped to the nearest dose group based on the dose they actually received. Thus, patients that receive a dose of < 75 U will be assigned to the 50 U treatment group, patients that received a dose in the range of ≥ 75 U and < 150 will be assigned to the 100 U treatment group, while patients that received ≥ 150 U will be assigned to the 200 U group (Table 1). Patients who received a different dose for any other reason than the 6 U/kg cap, will be analyzed according to the dose they were randomized to.

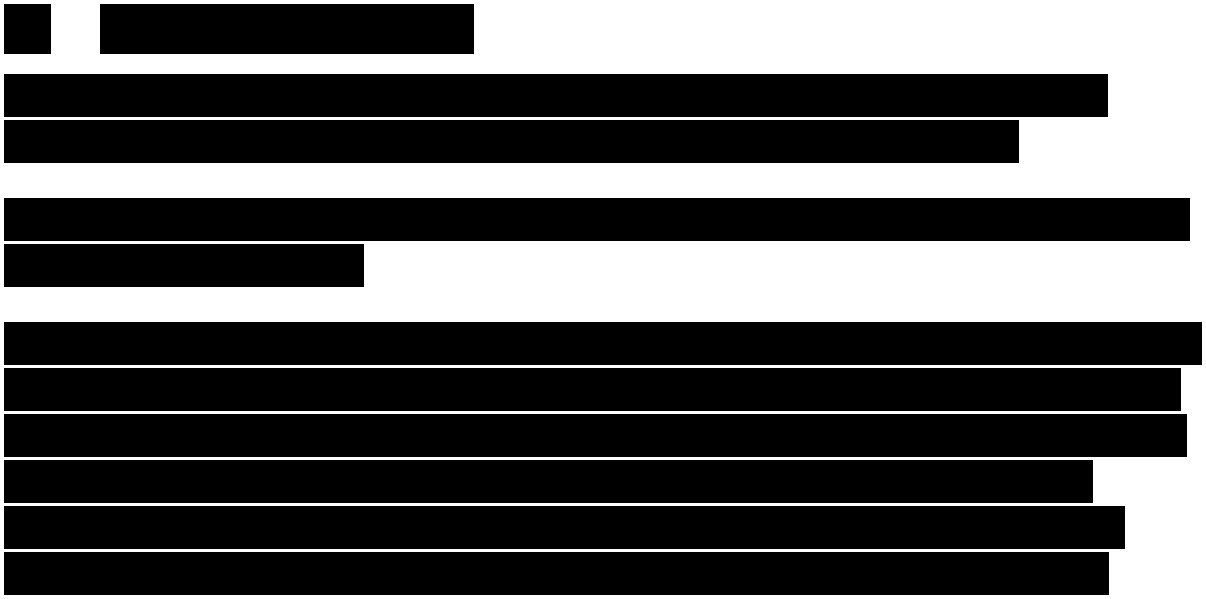
Safety Population

The safety population will include all patients who underwent the treatment procedure and received study drug on randomization/day 1. Safety analyses will be based on actual treatment received. Patients who received a different dose than the dose they were randomized to (as a result of either the 6 U/kg weight cap or any other reason) will be grouped according to the nearest dose group based on the actual dose received, as presented in Table 1.

2.1.1 Handling Mis-randomization and Mis-stratification

Treatment group assignment, in case of mis-randomization, is discussed in Section 2 above.

For any analysis that are by stratum or for analysis that adjusts for stratum effect, the actual strata will be used instead of the strata assigned at randomization.



2.3 Data Conventions

The following data conventions will be applied to all analyses.

- A patient's weight adjusted dose will be derived using the randomization information and the patient's actual weight provided in IVRS/IWRS at baseline.
- Unless stated otherwise, all statistical tests will be at a 2-sided significance level of 0.05. P-values ≤0.050 will be considered statistically significant.
- Since the qualification for retreatment may occur anytime from week 12 onwards, no statistical tests for pairwise comparison of treatment groups will be performed for any visit beyond week 12.
- The type III sums of squares will be used for all analysis of covariance models (ANCOVA).
- The variance for Kaplan-Meier estimates will be calculated using Greenwood's formula.
- Descriptive statistics for continuous variables include the sample size (N), mean, SD, median, minimum (min), first quartile (Q1), third quartile (Q3), and maximum (max).

- Summary statistics for categorical variables include the sample size (N), frequency count and percent.
- The Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used to code all adverse events (AEs) and medical history.
- World Health Organization Drug Dictionary Enhanced (WHO DDE) preferred name and MedDRA will be used to code all medications.
- Study duration from day 1 (injection date) will be calculated as:

  Study day in study = visit date – day 1 date + 1.
- For vital signs and laboratory summary tables, baseline is defined to be the last assessment prior to BOTOX injection.
- For by visit, vital signs and laboratory summary tables, there will also be a summary of the last post-baseline assessment.
- The algorithm presented in Table 3, together with the rules below will be used to impute incomplete or missing dates for adverse events and medications as follows:
  (a) AE start dates will be imputed as the minimum of the following:
    - initial imputed date, where target date = study drug injection date
    - complete end date

  (b) Medication start dates will be imputed as the minimum of the following:
    - initial imputed date, where target date = study drug injection date – 1
    - complete end date

  (c) AE and Medication end dates will be imputed as the minimum of the following:
    - initial imputed date, where target date = study exit date + 30
    - death date
- Concomitant medication will be classified using the following convention: 1) If the start date of medication is after or on study drug injection date, then it will be counted as concomitant medication; 2) If the start date of medication is prior to the study drug injection date and stop date is on or after study drug injection date, then it will be counted as both prior medication and concomitant medication.

- All partial dates (including AE, concurrent and prior medication) will be listed "as is" in the data listings.

Table 3 Initial Imputed Date Algorithm

Available Year (YYYY)	Available Month (MM)			
	Missing	**< Target Month**	**= Target Month**	**> Target Month**
Missing	Target Date	—		
< Target Year	YYYY-12-31	YYYY-MM-LD		
= Target Year	Target Date	YYYY-MM-LD	Target Date	YYYY-MM-01
> Target Year	YYYY-01-01	YYYY-MM-01		

YYYY = available start date year; MM = available start date month; LD = last day of the month.

2.3.1 Diary Data Conventions

- For baseline and post-treatment visits, analyses will be based on the diary data collected over two consecutive days. "Wake time information" will be collected for each diary day including the time the patient woke up in the morning and presence/absence of night time leaking by accident (from the previous night), as well as the time and volume of urine collected on the first morning catheterization. "Day time information" will be collected for each diary day including date, time, and type of voiding episode [leak by accident (i.e. urinary incontinence), urinated with catheter, urinated without catheter (i.e. voluntary void)] for each daytime episode (from time after waking up to start the day and doing the first morning catheterization, and going to bed to sleep for the night). Lastly, "bed time information" will be collected for each diary day including the time the patient went to bed for the night.

  - Note: Recording day time urinary events should begin *after* the 1st morning catheterization (as the urine expelled is from the previous night). In cases where the patient erroneously re-entered the first morning catheterization event as a day time event (ie, the time of 1st morning catheterization and the time of the first day time urinary event are the same), the event will not be included in the analysis for day time events.

- The visit windows [redacted] will be used to derive a patient's diary parameters for each visit.

  - A valid diary day is defined as a day where there are one or more urinary episodes of any type (incontinence, catheterization, or voluntary void) during the daytime

collection period. In the case of patients who provide just one valid diary day within a visit window, the 2-day frequency of daytime urinary incontinence will be prorated with the value from the valid diary day.

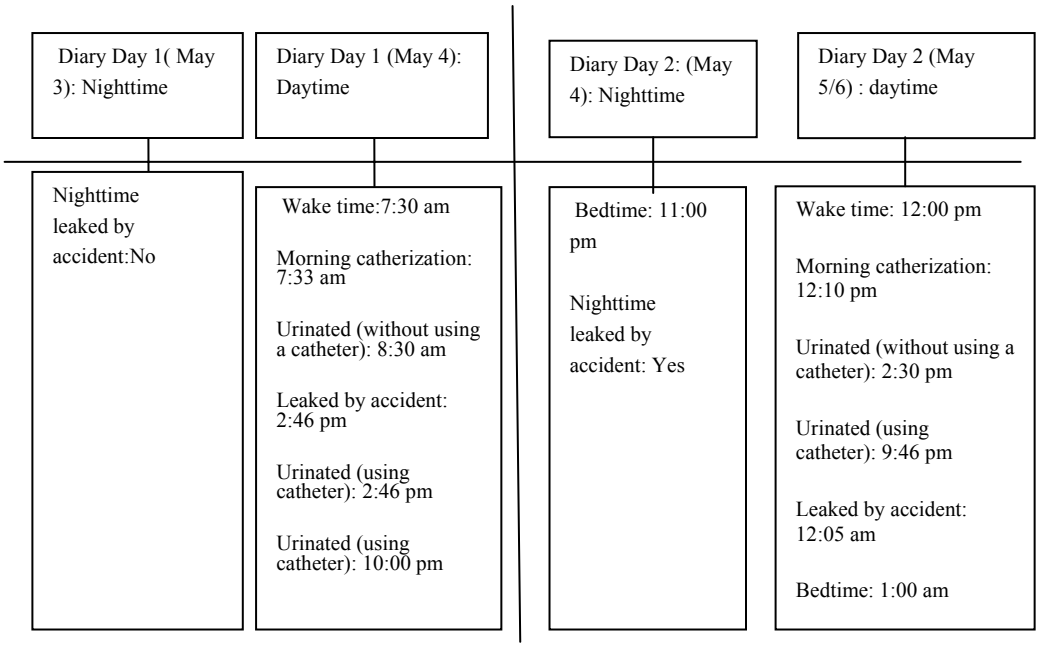
- If there are no valid diary days within the window, the 2-day diary data will be set as missing for the visit.

- For baseline and post-treatment visits, the 2-day diary will be determined based on the following algorithm:

  1) Apply visit windows [redacted] which are based on days from the date of study drug injection.

  2) Determine the time of the first daytime urinary episode that is within the visit window (in the example below, 8:30 am on May 4). Count forward two consecutive daytime dairy collection days. Note: the second daytime period should end within the window, i.e., prior to or on the last day specified in the window definition; otherwise, the nighttime or daytime data will not be used for the corresponding window. For baseline diary data, any urinary episodes collected up to the time of injection will be counted towards the baseline diary data.

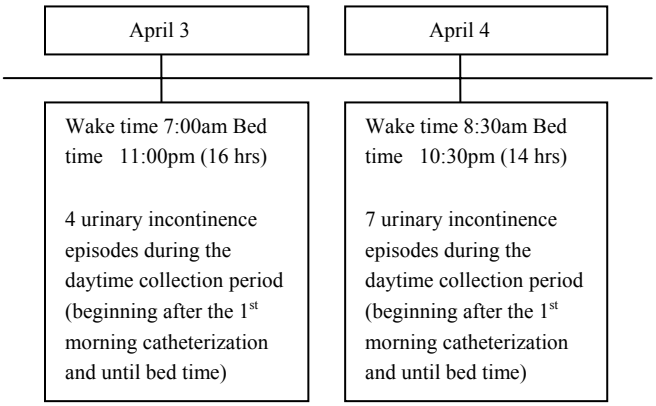
  3) Using the example below, the first daytime period (used to determine normalized day time period) starts with a wake time of 7:30 am on May 4 and ends with a bedtime of 11:00 pm (going to bed to sleep for the night). The bedtime for May 4 starts at 11:00 pm and ends at the wake time of 12:00 pm on May 5. The second daytime period starts on 12:00 pm on May 5 (wake time) and ends at 1:00 am May 6. Note that the wake time and bedtime can go over 2 calendar days. In the data set, for a given daytime, even if the daytime period goes over 2 calendar dates it will be recorded under the same calendar date. The time of the day will be used to accurately attribute the date of the event.



- Missing daily average frequency of episodes of daytime urinary incontinence at baseline will be imputed using the median of all non-missing values at baseline within the same treatment group. For the primary analysis, for scheduled diary assessments up to the week 6 visit [redacted], the missing daily average frequency of episodes of daytime urinary incontinence will be replaced using the last observation carried forward (LOCF) approach. For scheduled diary assessments after the week 6 visit, no imputation method will be applied.

- The daily frequency of daytime urinary incontinence episodes will be normalized to a 12-hour daytime period. The following normalization algorithm will be used:

  1) Apply visit window [redacted] which uses days from treatment as reference.
  2) Identify wake time and bedtime within the visit window. Daytime period (in hours) is determined by time between wake time and bedtime for that day.
  3) Using the example below, 4 urinary incontinence episodes are recorded during the first daytime period of 16 hours (7:00am to 11:00pm), and 7 episodes recorded during the second daytime period of 14 hours (8:30am to 10:30pm).



On a given day, the number of daytime urinary incontinence episodes normalized to a 12-hour daytime period will be calculated by

$$\frac{12}{\text{daytime period}} \times \text{number of daytime urinary incontinence episodes},$$

which, in the example, adjusts to 3 (= (12/16) × 4) and 6 (=(12/14)× 7) normalized urinary incontinence episodes, respectively. The daily average frequency of daytime urinary incontinence episodes by the normalized daytime period in a given visit window will be 4.5 (= (3 + 6)/2) in this example.

- If wake time is missing, the missing wake time will be imputed by the first morning catheterization where urine volume is collected. If both the wake time and the first morning catheterization are missing then the morning wake time will be imputed by either the first urinary episode time of any type recorded on that day or 7:00 am, whichever comes earlier. If bedtime is missing, the missing time will be imputed by either the last urinary episode time of any type recorded on that day or 10:00 pm, whichever comes later.

3. Disposition and Exit Status

3.1 Screening Log Data

A listing of patients that screen failed will be generated for patients that signed informed consent. The listing will include information on demographic characteristic (sex, race and age) and reason for screen failure.

3.2 Disposition and Exit Status

The patient disposition table for this study will be based on the mITT population. A listing of patients' disposition information will also be generated. This patient listing will also include information on the study duration.

3.3 Study Duration

In this study patients only get one injection of study drug hence, the duration of exposure to study treatment and study duration will be the same. For details on how to analyze duration of exposure to study treatment see [redacted]

3.4 Protocol Deviations

Significant and non-significant deviations are defined in the Protocol Deviations Specification Document and will be determined prior to database lock. A by patient protocol deviation listing will be produced for the significant protocol deviations. The deviation type and detail will be presented.

4. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be analyzed using the mITT population. Baseline assessments are defined to be assessments taken prior to study drug injection.

4.1 Demographics

Age, race, sex, weight (kg) and height (cm) will be summarized by treatment group and overall. Race will be summarized as Caucasian, Black, Asian, Hispanic, and Other.

4.2 Disease Characteristics

The following baseline information will be summarized using the mITT population:

- baseline information on stratification factors (age < 12 vs ≥ 12 years; daytime urinary incontinence ≤ 6 vs. > 6 episodes),
- baseline bladder characteristics (presence or absence of open bladder neck, external sphincter dyssynergia, fecal incontinence, bladder sensation with filling, and whether or not the patient is ambulatory),
- baseline bladder wall thickness

- use of anticholinergic therapy at baseline (on day of injection),
- number of prior anticholinergic therapy used for urinary incontinence
- duration of prior anticholinergic therapy used for urinary incontinence
- reason prior anticholinergic therapy not considered to adequately managed urinary incontinence
- daily average frequency of normalized daytime urinary incontinence episodes,
- daily average urine volume at first morning catheterization (mL),
- presence/absence of night time urinary incontinence,
- number of urinary tract infection (UTI) within 6 months prior to screening
- A patient's neurological characteristics, and
- urodynamic assessments namely, presence or absence of involuntary detrusor contraction (IDC), maximum cystometric capacity (MCC) (mL), maximum detrusor pressure during the first IDC ($Pdet_{Max1stIDC}$) (cm H_2O) if IDC present, maximum detrusor pressure ($Pdet_{Max}$) (cm H_2O) during the storage phase, and detrusor leak point pressure (DLPP) (cm H_2O).

4.3 Prior Medications

Prior medications are defined as any medications which are administered prior to the BOTOX injection. The mITT population will be used for the analysis of prior medications.

4.3.1 Prior Anticholinergic Medications for Urinary Incontinence

The frequency and percentage of prior anticholinergic medications for urinary incontinence will be summarized by WHO Drug Class and WHO DDE preferred drug name. A summary of the primary reason for not being adequately managed by prior anticholinergic medication will also be presented.

4.3.2 Antibiotic Medication for Prophylactic Treatment

All prophylactic antibiotic medication associated with study drug treatment will be summarized by WHO Drug Class and WHO DDE preferred drug name. Such medications will not be classified as either prior or concomitant medication.

4.4 Concomitant Medications/Procedures

A concomitant medication is any medication which is administered any time after the study drug injection, irrespective of when the medication started or stopped.

4.4.1 Concomitant Anticholinergic Medications for Urinary Incontinence

Concomitant anticholinergic medication for urinary incontinence will be summarized by WHO Drug Class and WHO DDE preferred drug name as described for the prior medication using the mITT population.

4.4.2 Concomitant Medication

Concomitant medications will be summarized by by WHO Drug Class and WHO DDE preferred drug name as described for the prior medication using the mITT population.

4.4.3 Concurrent Procedures

A patient listing of concurrent procedures will be produced using the mITT population.

4.5 Past Medical History

Medical history information will be coded with the MedDRA dictionary. Frequencies and percentages will be summarized by MedDRA primary System Organ Class (SOC) and preferred term for the mITT population.

5. Efficacy Analyses

Efficacy analyses will be performed on the mITT population. The primary time point for efficacy will be week 6. Efficacy data will also be presented by study visit using the visit windows [redacted].

5.1 Collection of Primary Efficacy Measurement(s) and Derivation of Primary Efficacy Variable(s)

The primary efficacy variable is the change from baseline to post-treatment in the normalized daily average frequency of daytime urinary incontinence episodes (daytime is defined as the time between waking up to start the day and 1st morning catheterization, and going to bed to sleep for the night). The daily average frequency of daytime urinary incontinence episodes is obtained using the total number of daytime urinary incontinence episodes recorded in a 2-day bladder diary divided by 2, and baseline frequency is defined as the daily average frequency of episodes of daytime urinary incontinence preceding the study treatment (ie, obtained from the screening diary).

Each daytime period recorded in the bladder diary is normalized to represent a 12-hour period to account for differing durations of the daytime period between and within different patients (see Section 2.3 for further details). Furthermore, if there is just 1-day of valid bladder diary data, this will be used as the daily average frequency of daytime urinary incontinence episodes (see Section 2.3 for further details).

The primary time point for this change from baseline endpoint will be week 6 posttreatment.

5.2 Primary Efficacy Analyses

5.2.1 Primary Analyses of Primary Efficacy Variable

For each of the BOTOX doses of 200 U and 100 U, the null hypothesis is that there is no difference between that dose group and the 50 U BOTOX dose group in mean change from baseline in daily average frequency of daytime urinary incontinence episodes at week 6. The alternative hypothesis is that there is a difference in mean change from baseline in daily average frequency of daytime urinary incontinence episodes between the higher BOTOX dose group under consideration and the 50 U dose group at week 6.

The hypotheses will be tested using an ANCOVA model with baseline value as covariate and treatment group, age (< 12 years or ≥ 12 years), baseline daytime urinary incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day diary collection period), and use of anticholinergic therapy (no/yes) at baseline (on day of injection) as factors. Furthermore, the last observation carried forward (LOCF) method of imputation will be used to impute missing week 6 assessments. The fitted model will be used to derive the adjusted mean treatment differences in the primary variable (least-squares [LS] mean difference) and

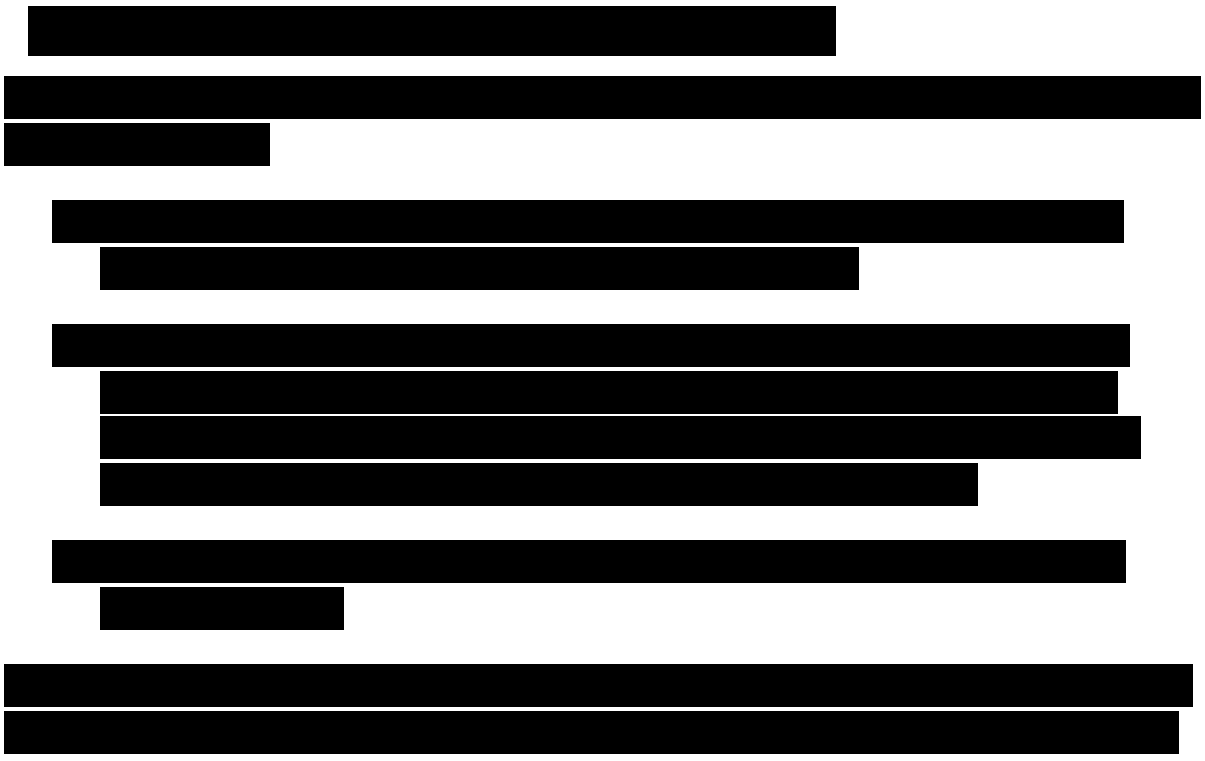
associated 95% CI, for the comparison of the 50 U BOTOX treatment group versus the 200 U and 100 U BOTOX treatment groups.

After fitting the ANCOVA model, to adjust for multiplicity, a hierarchical analysis testing strategy (Lubsen and Kirwan, 2002) will be applied. Initially the 200 U versus 50 U BOTOX mITT treatment group will be tested at a two sided significance level of 5%. If it is concluded that the 200 U BOTOX treatment group has a greater mean reduction in daily average frequency of daytime urinary incontinence episodes, the 100 U versus 50 U BOTOX treatment group will be tested. In other words, results of hypothesis testing for 100 U versus 50 U BOTOX will only be considered for statistical significance if the treatment difference for 200 U versus 50 U BOTOX is shown to be statistically significant.

Furthermore, the average daytime duration will be summarized for each visit.

Apart from the hierarchical testing, the analysis outlined above will also be repeated for the week 2, and 12 visit diary assessments. No imputation method will be applied in these analyses.

For each post-baseline visit, the primary efficacy variable will also be summarized for each treatment arm using mean, median, standard deviation, min, max and t-distribution based 95% confidence interval.



[redacted]

[redacted]

5.3 Secondary Efficacy Analyses

The following secondary efficacy variables that are based on patient diary data will be assessed.

- the percentage of patients that have a ≥50%, ≥75%, ≥90%, and 100% reduction from baseline in the number of normalized daytime urinary incontinence episodes
- change from baseline in average urine volume at first morning catheterization (mL)
- presence or absence of night time urinary incontinence

The following secondary urodynamics efficacy variables will be assessed at week 6 posttreatment

- change from baseline in maximum cystometric capacity (mL) (MCC)
- The proportion of patients with presence of involuntary detrusor contraction (IDC)
- if an IDC is present, change from baseline in maximum detrusor pressure during the first IDC ($Pdet_{Max1stIDC}$) (cm H_2O)
- change from baseline in maximum detrusor pressure ($Pdet_{Max}$) (cm H_2O) during the storage phase
- if leak occurs, change from baseline in detrusor leak point pressure (DLPP) (cm H_2O)

No imputation will be used for the missing values of secondary efficacy variables. A hierarchical analysis strategy to adjust for multiplicity will not be implemented.

5.3.1 Analysis of the Number of Patients that have Reduction from Baseline in Daytime Urinary Incontinence Episodes that Meet Certain Thresholds

The number of patients that have reduction from baseline in daily average frequency of normalized daytime urinary incontinence episodes [redacted]

5.3.2 Urine Volume at First Morning Catheterization (mL)

For urine volume at first morning catheterization (mL), the mean baseline, mean raw values and mean change from baseline at each visit and associated 95% CI for the mean change from baseline will be derived for each treatment group. For visits up to week 12 posttreatment, an ANCOVA model similar to the primary ANCOVA model will be fitted to the change from baseline value. The model will include the baseline value as covariate and treatment groups, age (< 12 years or ≥ 12 years), baseline daytime urinary incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day diary collection period), and anticholinergic therapy use(no/yes) at baseline as factors. The resulting adjusted treatment difference (LS mean difference) and associated 95% CI of the treatment difference in mean change from baseline will be derived for the comparison of the higher BOTOX dose groups versus the 50 U BOTOX group.

5.3.3 Presence or Absence of Night Time Urinary Incontinence

For the analysis of night time urinary incontinence, the numbers (percentage) of patients who experienced night time urinary incontinence on 0, 1, or 2 nights will be presented at study baseline and at each visit.

5.3.4 Analysis of Urodynamics Parameters

Urodynamics parameters are only assessed at screening (baseline) and at week 6 posttreatment. For urodynamic parameters only the central reviewer's assessment will be analyzed.

For the following urodynamics parameters:

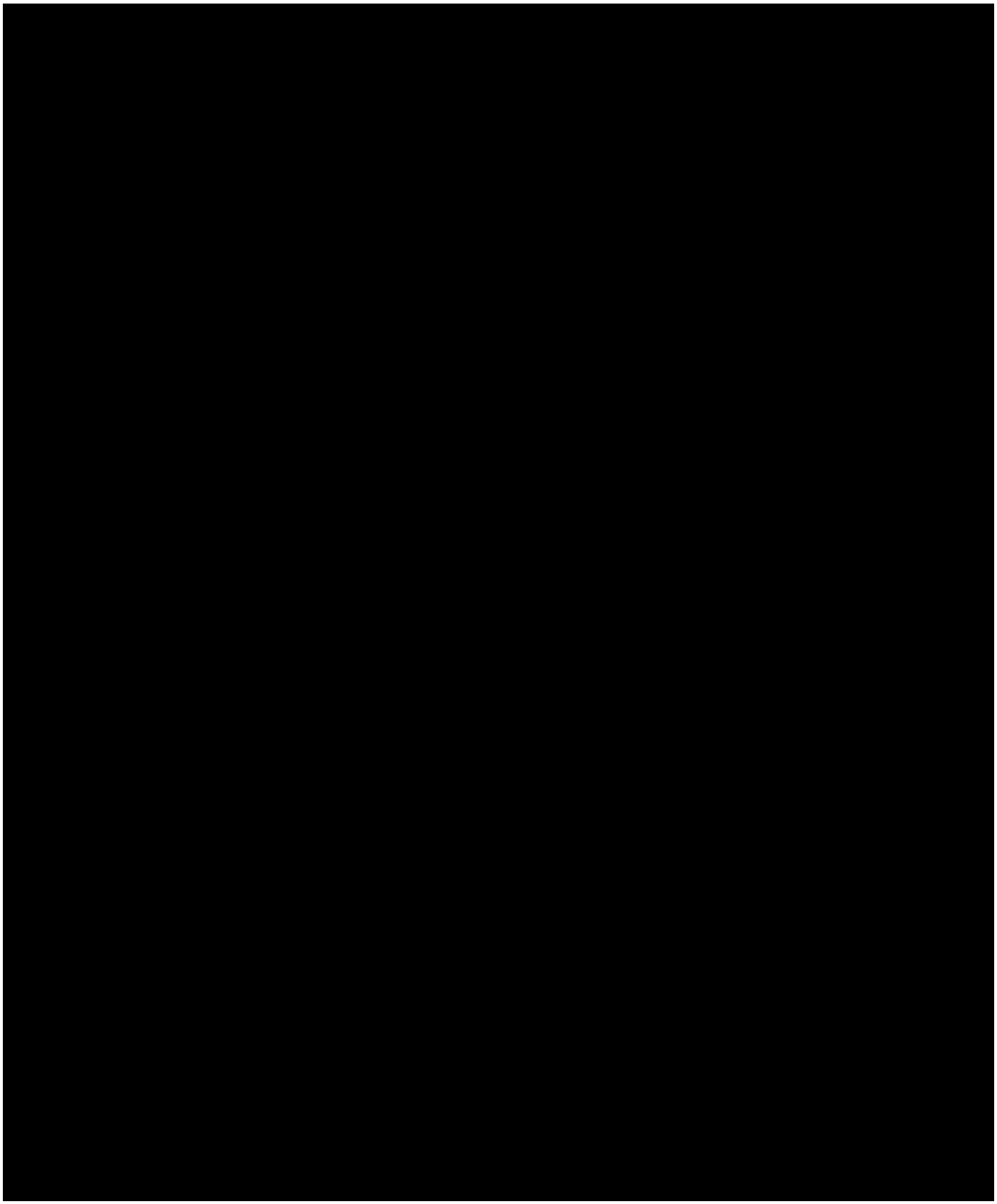
1. maximum cystometric capacity (mL) (MCC),
2. maximum detrusor pressure ($Pdet_{Max}$) during the storage phase (cm H_2O),
3. if IDC is present, maximum detrusor pressure ($Pdet_{Max1stIDC}$) during the first IDC (cm H_2O), and
4. if leak occurs, detrusor leak point pressure (DLPP) (cm H_2O) ,

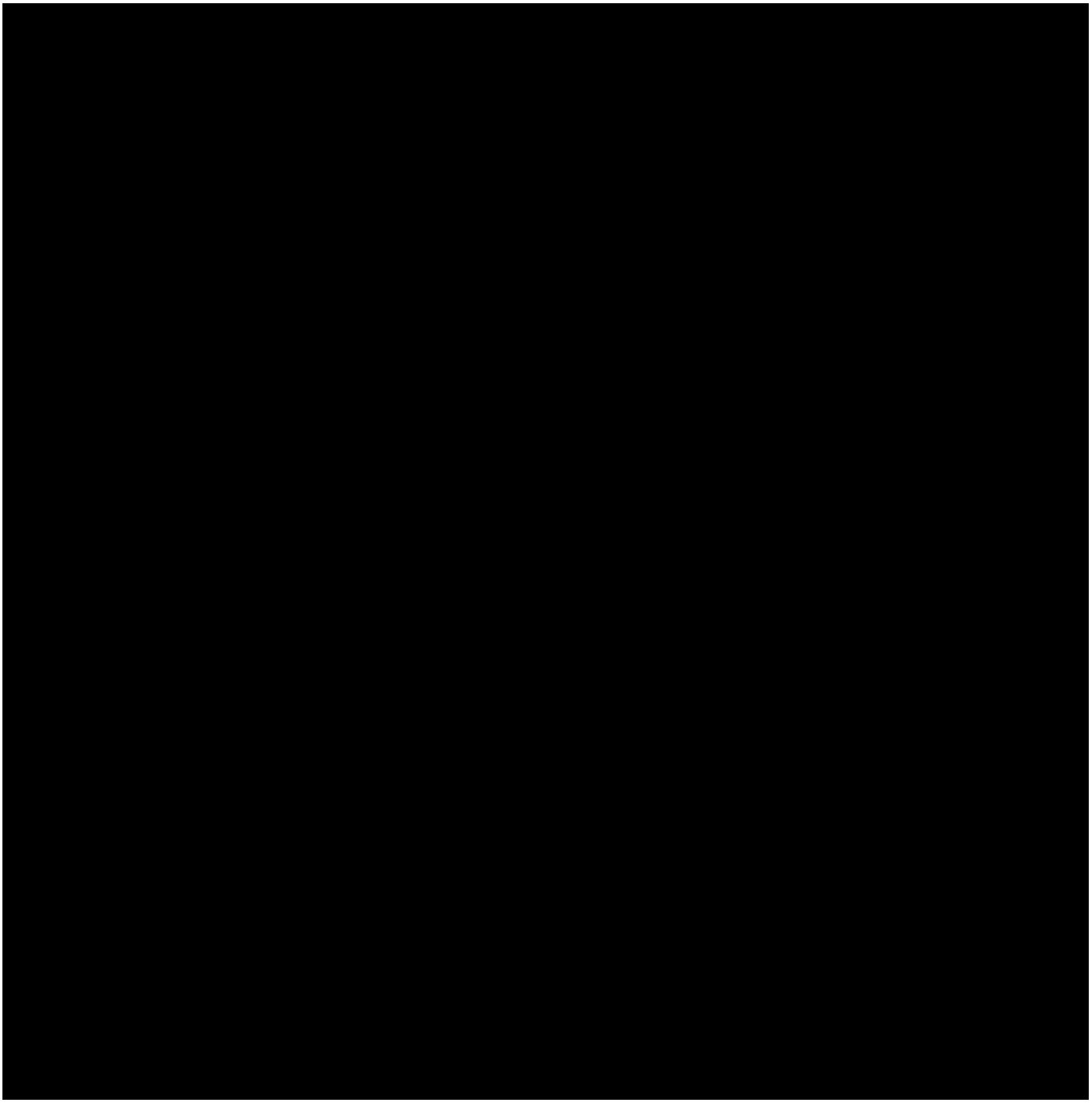
values at the two visits (baseline and week 6) and change from baseline values for week 6 posttreatment will be summarized. Furthermore, an ANCOVA model will be fitted and used to derive adjusted treatment means and treatment difference estimates for the comparison of the lower dose (50 U) with the higher BOTOX dose groups. The explanatory variables in the model will include the same explanatory variables listed for the primary efficacy variable analysis however, the covariate will be the baseline effect for each parameter under consideration.

For urodynamics parameter #3, change from baseline value can only be derived when maximum detrusor pressure ($Pdet_{Max1stIDC}$) during the first IDC is present at both baseline and post-baseline visit (ie, an IDC occurs at both baseline and at week 6). Similarly, for urodynamics parameter #4, change from baseline value can only be derived if a leak occurs during the urodynamics procedure at both baseline and week 6 visit. In both cases (analysis of #3 and #4), if less than 25% of the mITT patients have change from baseline values, the ANCOVA model may not be fitted.

The number (percentage) of patients with presence of an IDC at baseline and at week 6 posttreatment will be summarized by treatment groups. Associated 95% confidence interval will also be generated. The difference at baseline and at week 6 posttreatment in the proportions of patients with presence or absence of an IDC between the treatment groups will be analyzed using the CMH methodology as described for the analysis of percentage patients meeting a threshold of reduction in daytime urinary incontinence episodes [redacted].

[redacted]





5.5.2 Duration of Effect

Duration of treatment effect will be evaluated by treatment group by assessing the following two variables.

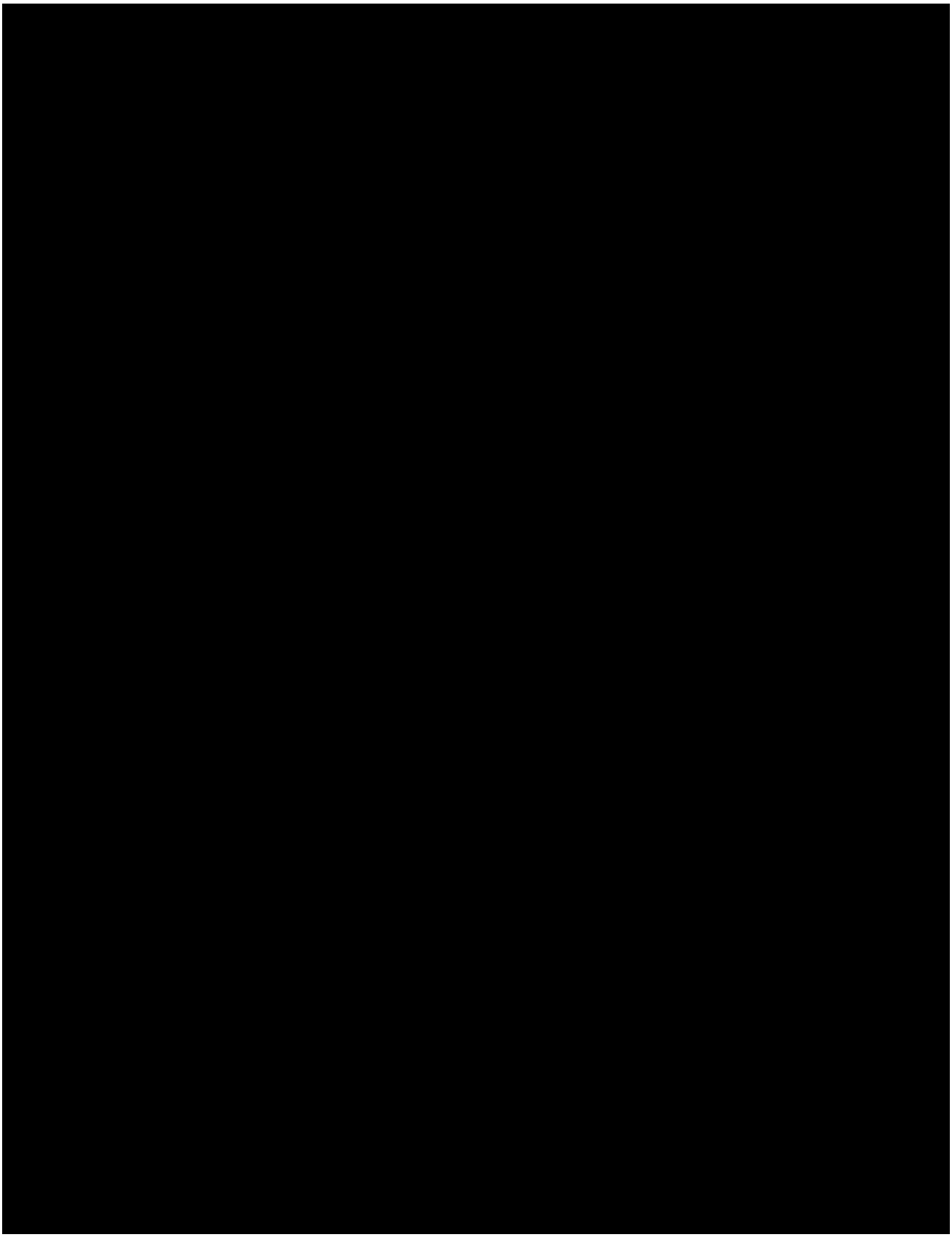
- Time between study drug injection (injection) and patient's first request for retreatment

- Time between study drug injection (injection) and qualification for retreatment (study exit date for patients that requested and qualified for retreatment)

Patients who did not request retreatment will be treated as censored at the time of study exit.

For each treatment group, the Kaplan-Meier survival methodology will be used to estimate the median time to request for re-treatment. Furthermore, the 25th and 75th percentiles of the time to request for re-treatment will be estimated. The associated 95% CIs will also be presented for each treatment group. The proportion of patients requesting re-treatment during the study will also be presented.

The time to qualification for re-treatment will be summarized in a similar manner.



[redacted]

6.2 Adverse Events

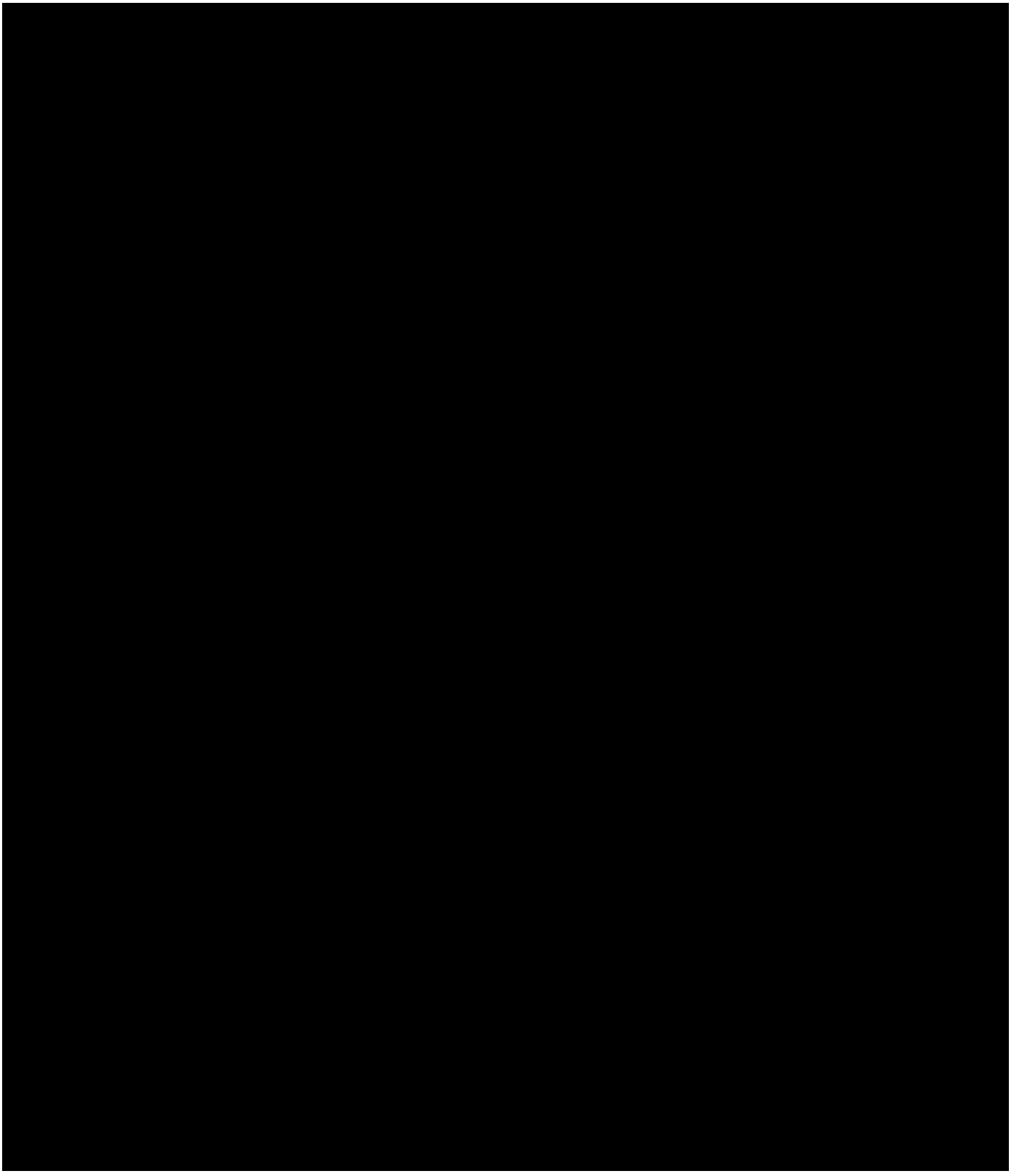
Adverse events (AEs) will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

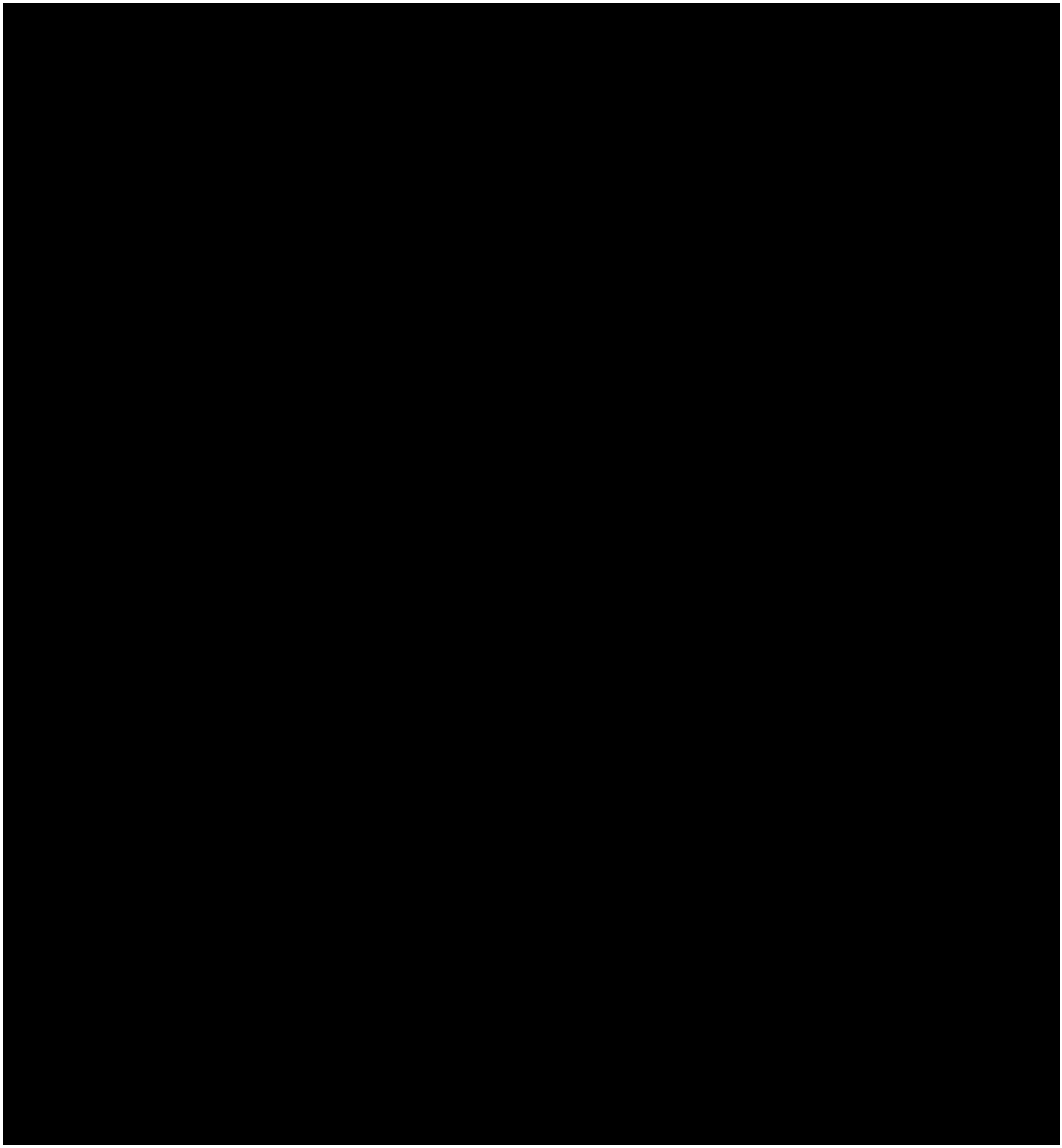
Pre-treatment AEs are AEs that have start date on or after the signing of consent form and prior to the BOTOX injection.

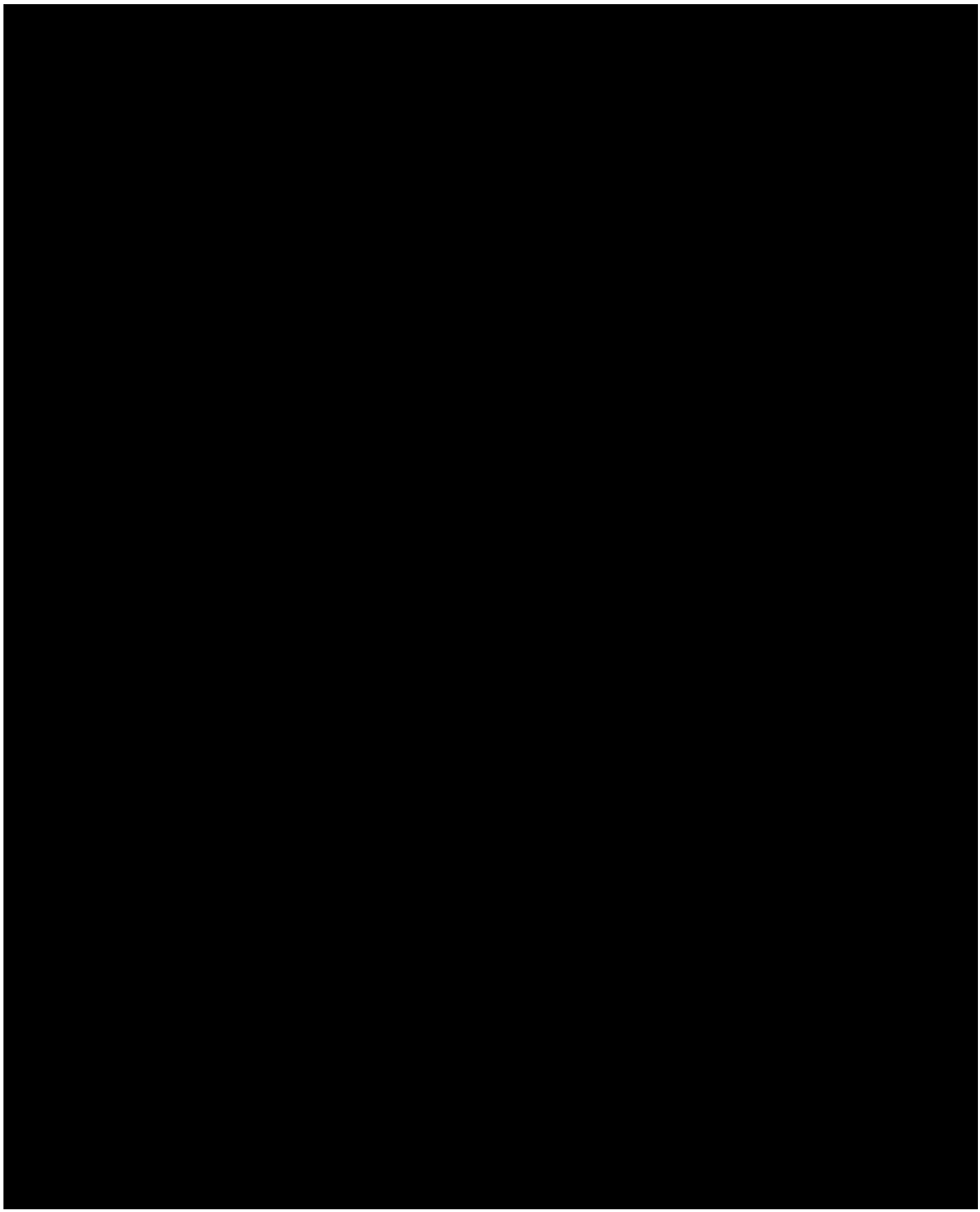
An AE will be considered a treatment-emergent adverse event (TEAE) if it was present after the first dose of study treatment or was present before the date of the first dose of study treatment and increased in severity or became serious after the first dose of study treatment.

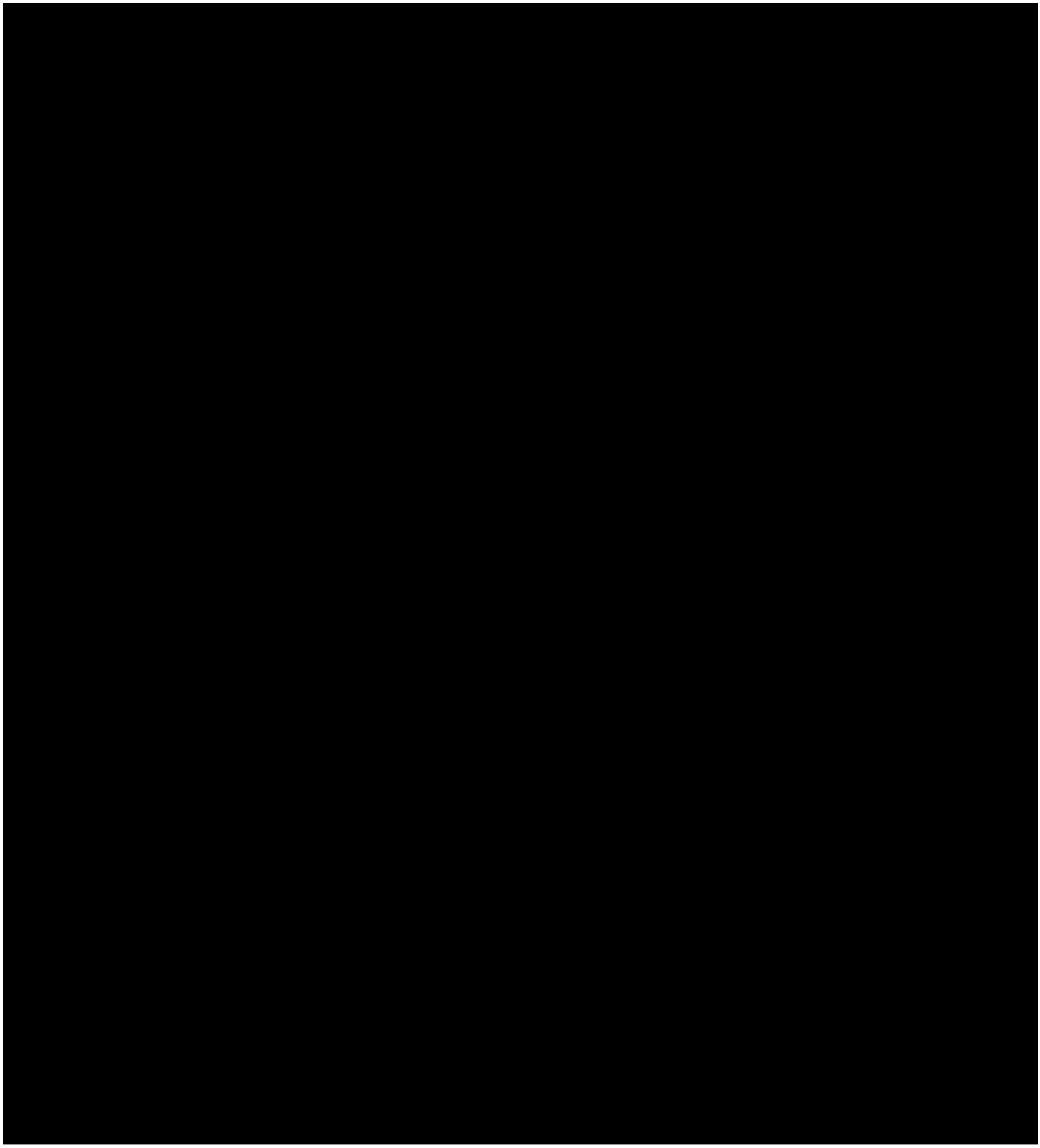
The number and percentage of patients reporting TEAE in each treatment group will be tabulated by descending percentage in any group, by system organ class and preferred term, and further categorized by severity and causal relationship to the study drug and study drug injection procedure. If more than 1 AE is coded to the same patient, the patient will be

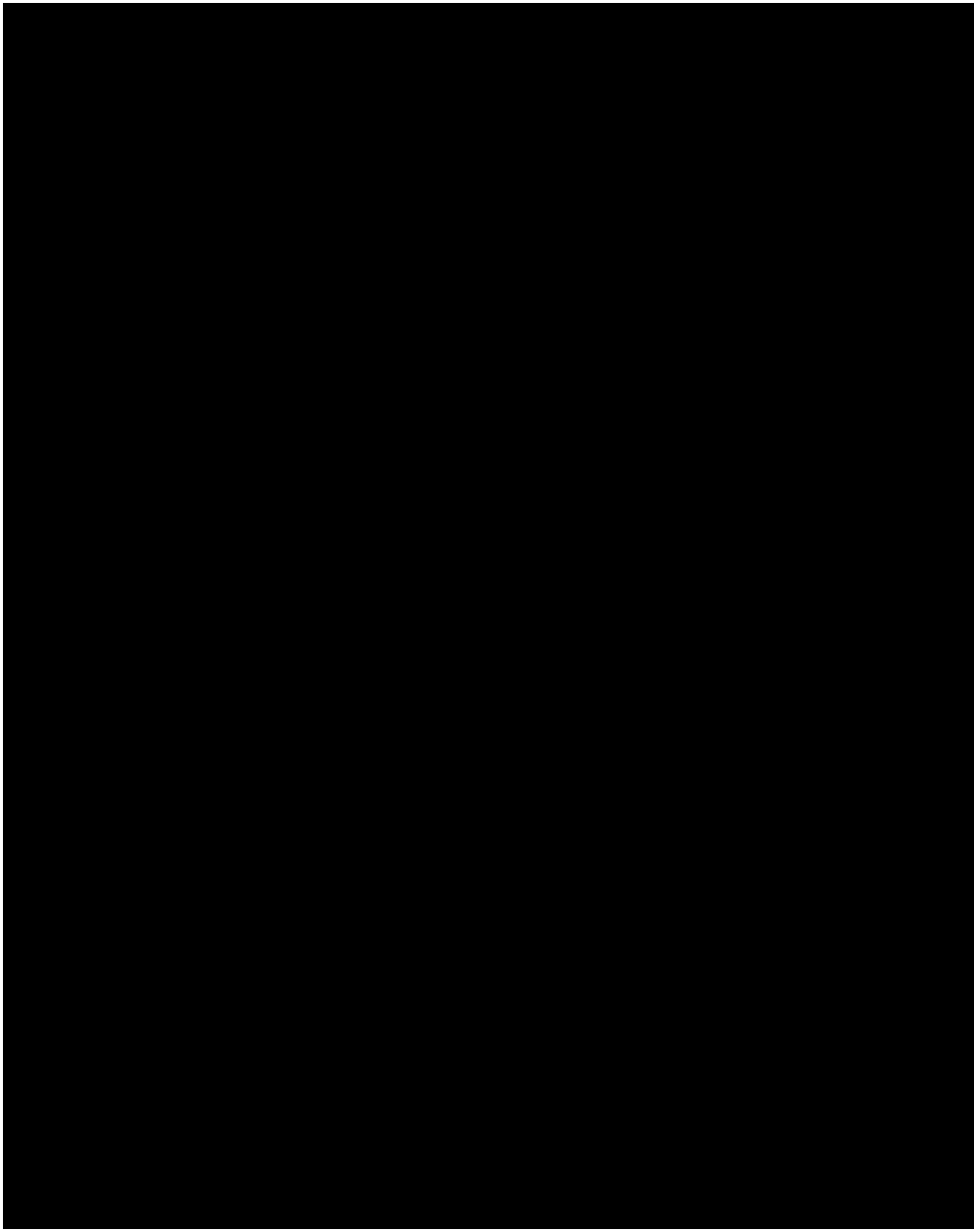
counted only once for that preferred term using the greatest severity for the summarization by severity and causal relationship.











9. Interim Analyses

No interim analysis is planned for this study. However, there is a Data Review Committee (DRC) that reviews, on regular bases, selected blinded safety analyses. There is a separate DRC charter and analysis plan that outlines the function of the DRC and what they will be reviewing.

10. Analysis for US FDA

Not applicable.

11. Data Collected but not Analyzed

A patient's surgical history and female patients' birth control treatment during the study are collected in this study. No output will be generated for these data.

12. Deviations from Protocol

There are no deviations from the protocol.

13. References

Lubsen J, Kirwan BA. Combined endpoints: can we use them? Statistics in Medicine. 2002;21(19):2959-2970.

Mallinckrodt CH, Clark WS, David SR (2001a). Type I error rates from mixed-effects model repeated measures versus fixed effects analysis of variance with missing values imputed via last observation carried forward. Drug Information J. 2001a;35:1215-1225.

Mallinckrodt CH, Clark WS, David, S. R. (2001b). Accounting for dropout bias using mixed-effects models. J. Biopharmaceutical Statistics. 2001b;11:9-21.

Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol. 2009;4:1832-1843.

14. SAP Amendments

Following is a summary of content-oriented changes that were made to each section of the SAP, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

14.1 Amendment 1 Summary

Sections	Revision	Rationale
Section 2.1: Analysis Populations	Deleted Per-protocol population. All analyses on per-protocol population were also deleted in other sections.	To reflect current company standard for not performing analyses on per-protocol population for superiority trials.
Section 2.3: Data Conventions	Modified imputation rules for completely missing or partial dates for adverse events and prior/concomitant medications	To reflect current company standard
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 6.2.1: [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 6.4. Vital Signs	Sections was re-written to reflect current company standard	To reflect current company standard

14.2 Amendment 2 Summary

Sections	Revision	Rationale
Section 2.1: Analysis Populations	Additional text included to clarify how participants are assigned to actual BOTOX treatment group based on actual dose administered.	To clarify how participants are assigned to actual BOTOX treatment group based on actual dose administered.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

14.3 Amendment 3 Summary

Sections	Revision	Rationale
Section 2.1: Analysis Populations	The following text: *"If the "incorrect unit dose administered" is not populated in the eCRF, then the randomized dose (ie, 50U, 100U, or 200U) and the patient's weight at the screening visit will be utilized to determine the actual dose administered as described in section 12.1 of the study protocol."* was replaced with *"If the "incorrect unit dose administered" is not populated in the eCRF, then the randomized dose (ie, 50U, 100U, or 200U) and the patient's weight recorded in IVRS/IWRS at the time of randomization will be utilized to determine the actual dose administered as described in section 12.1 of the study protocol."*	To clarify that patients weight used in this derivation will be taken from IVRS/IWRS records.
Section 2.3.1: Diary Data Convention	The text in the first bullet point was modified to make it clearer to understand. The following new paragraph was added: *Note: Recording day time urinary events should begin after the 1st morning catheterization (as the urine expelled is from the previous night). In cases where the patient erroneously re-entered the first morning catheterization event as a day time event (ie, the time of 1st morning catheterization and the time of the first day time urinary event are the same), the event will not be included in the analysis for day time events.*	To clarify how this diary entry errors made by patients during the study should be handled during analysis.
Section 5.3.3: Presence or Absence of Night Time Urinary Incontinence	Deleted the following text: *For each visit there will be two sets of percentages. The first set of percentage will be for patients that have just one valid diary day and the second set will be for patients that have two diary days i.e., the numerator for the percentage calculation will be the patients that have the given number of diary days.*	Makes it much easier to understand the summary to be presented here.

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Analysis Plan for Study 120 Amendment 3