NCT01852058

Study ID: 191622-121

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

Statistical Analysis Plan Amendment 2 Date: 20-Feb-2019

Allergan
Biostatistics
Analysis Plan – Clinical Study Report

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Final Analysis

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1. Introduction

This document details the planned analyses for study 191622-121. Patients that complete study 191622-120 are eligible to enroll into study 191622-121. The purpose of study 191622-121 is to further evaluate the long-term safety and efficacy of BOTOX for the treatment of urinary incontinence due to neurogenic detrusor over activity (NDO) in patients 5 to 17 years of age.

When all patients in study 191622-120 exit the study, there will be a data base lock (DBL) for study 191622-120 and a subsequent interim DBL and CSR for study 191622-121. The second and final analysis will occur when all patients exit study 191622-121. A final CSR will be completed at this time.

Data from Study 191622-121 will be integrated with the corresponding patient data from their participation in the preceding Study (191622-120). Patients who have received at least 1 BOTOX treatment since the start of their overall clinical study participation, i.e. either in study 191622-121 or the preceding study 191622-120, will be included in the analysis. This BOTOX-treated population will be used for all the statistical analyses and results presented by BOTOX treatment cycle. Patients who participated only in Study 191622-120 and did not participate in Study 101622-121 will not be included.

On completion of the interim analysis, the study will be unblinded to Allergan personnel. Study sites will be unblinded upon finalization of the interim clinical study report.

1.1 Primary Study Objectives and Design

The objective of study 191622-121 is to evaluate the long-term 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.

This is a long-term extension study to the preceding study, 191622-120. Patients will roll over directly from the preceding study; the exit visit of study 191622-120 is also the entry visit for study 191622-121. Patients exit study 191622-120 once they have qualified for retreatment or at week 48 if they never qualified. For the first retreatment in study 191622-121, the qualification may have occurred in study 191622-120.

In this study, patients can receive multiple injections of the following doses:

- 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.

The dose received at any given treatment will be determined by the investigator based on the response to the preceding blinded treatment. The investigator can elect to keep the dose the same or increase the dose compared to the preceding treatment. If it is deemed a decrease in dose is warranted, the patient would be exited from the study. The actual dose received remains blinded unless the patient is requested to exit the study via the IVRS, as described at the end of Section 5.5 of the protocol or until the interim analysis of this study has been reported.

Patients in this study are evaluated at scheduled visits at 2, 6, and 12 weeks after each retreatment (week 2, 6 and 12 visits). After week 12 visit (12 weeks from the re-treatment), there are alternating telephone and clinic visits every 6 weeks until they qualify for further retreatment or exit the study. Request for retreatment can occur at any scheduled clinic or telephone visit, or between scheduled visits. If a request occurs at a scheduled clinic visit, this then becomes a qualification for retreatment visit, otherwise a qualification for retreatment clinic visit should occur within approximately 1 to 2 weeks of request.

Patients exit this study once 48 weeks have elapsed from the time of entry into the study and at least 12 weeks follow-up has occurred after their last BOTOX injection. Hence, for patients that did not prematurely exit the study, the study exit will be between 48 and 60 weeks after entry into this study; the latter being for patients who received retreatment at Week 48.

The efficacy measure that is of key interest is daytime urinary incontinence episodes, and the key time point is week 6 after each treatment.

1.1.1 Sample Size

For this long-term extension study, no formal sample size calculation was used. Approximately 78 patients are anticipated to roll over into this study, which is assuming approximately 76% of patients randomized into Study 191622-120 will be available and willing to participate in this study.

1.2 Secondary and Other Objectives

Not applicable.

1.3 Experimental Unit and Analysis Unit

The experimental unit in this study is a study subject. The efficacy measure of key interest is daytime urinary incontinence episode measured at a subject level.

2. Analysis Populations and Data Conventions

In order to maintain blinding of the BOTOX dose received, the drug is reconstituted by an independent drug reconstitutor (IDR). 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 trigger completion of the "Incorrect Unit Dose Administered" form by the IDR and the "incorrect unit dose administered" will be entered into the electronic case report form (eCRF).

2.1 Analysis Populations

One analysis population will be used in the statistical analysis of this study namely, the BOTOX-treated population.

BOTOX-treated population will include all patients that enrolled into study 191622-121 after receiving BOTOX injection in study 191622-120. A patient is considered to have enrolled in study 191622-121 if in study191622-120, in the extension eCRF page, it is marked that a patient will continue into study 191622-121.

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

For cycle based analysis, since the patient's dose can be increased in a blinded fashion from one cycle to the next, the analysis will be based on actual treatment received during that cycle and will be assigned to the nearest dose group per Table 1 above. As a result of either the 6 U/kg weight cap or site error, patients may not receive the dose assigned per the IWRS (interactive web response system).

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 per IWRS (ie, 50U, 100U, or 200U) and the patient's weight at the qualification for retreatment visit 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.

For analysis that is not cycle based (e.g. baseline and disease characteristics), the summary will be by the overall BOTOX -treated population and by what the BOTOX- treated patients received in Cycle 1, which also coincides with the Study 191622-120 safety treatment groups. In this document these treatment groups will be referred to as Cycle 1 treatment groups.

2.1.1 Handling Mis-randomization and Mis-stratification

Treatment group assignment, in case of patients who received incorrect dose is discussed in Section 2.1 above.

2.2 Analysis Visit Windows

All by visit analysis will be by visit window. The target day and visit window for each treatment cycle will be referenced to days after treatment/injection. The visit window for each treatment cycle is defined as follows:

[(target day of current visit + target day of previous visit)/2+1] to [(target day of current visit + target day of next visit)/2]

[redacted] For safety variables if there are multiple assessments in a given window, the value collected from the visit closest to the target day will be used to represent the window. If, instead of a single closest visit, 2 visits with values are equidistant (but not on the same day) from the target day, the latest visit will be used. If there are multiple observations on the same day the average of the observations will be used. For laboratory variables, this rule will be applied separately for each laboratory parameter.

2.3 Data Conventions

The following data conventions will be applied to all analyses.

- Baseline and study baseline are used interchangeably throughout this document. They both refer to baseline information collected at the start of study 191622-120.
- In general, metric systems will be used (e.g., kilograms (kg) and centimeters (cm)) and clinical laboratory data will be presented with the Standard International (SI) units.
- 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 histories.
- World Health Organization Drug Dictionary Enhanced (WHO DDE) preferred name and MedDRA will be used to code all medications.
- Cumulative study duration from Day 1 (first injection date in preceding study 191622-120) will be calculated as:

  Study day in study = visit date – day 1 date + 1.

- Cycle duration for a given Treatment X (i.e., Xth injection cycle where X > 1)will be calculated as:

  Study day of cycle X = visit date – day 1 of Treatment X + 1.

- 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 = first study drug injection date if the AE started in study 191622-120; exit day in study 191622-120 if the AE started in study 191622-121.
  - complete end date

  (b) Medication start dates will be imputed as the minimum of the following:

  - initial imputed date, where target date = first study drug injection date – 1 if the medication started in study 191622-120; exit day in study 191622-120 if the medcation started in sudy 191622-121.
  - 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. The exit date to be used will depend on when the AE (or medication) ended. If it ended in study 191622-120, the study 191622-120 exit date will be used. In contrast, if it ended in study 191622-121, the study 191622-121 exit date will be used.
- death date

- Concurrent 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		

2.3.1 Data Conventions Limited to Diary data

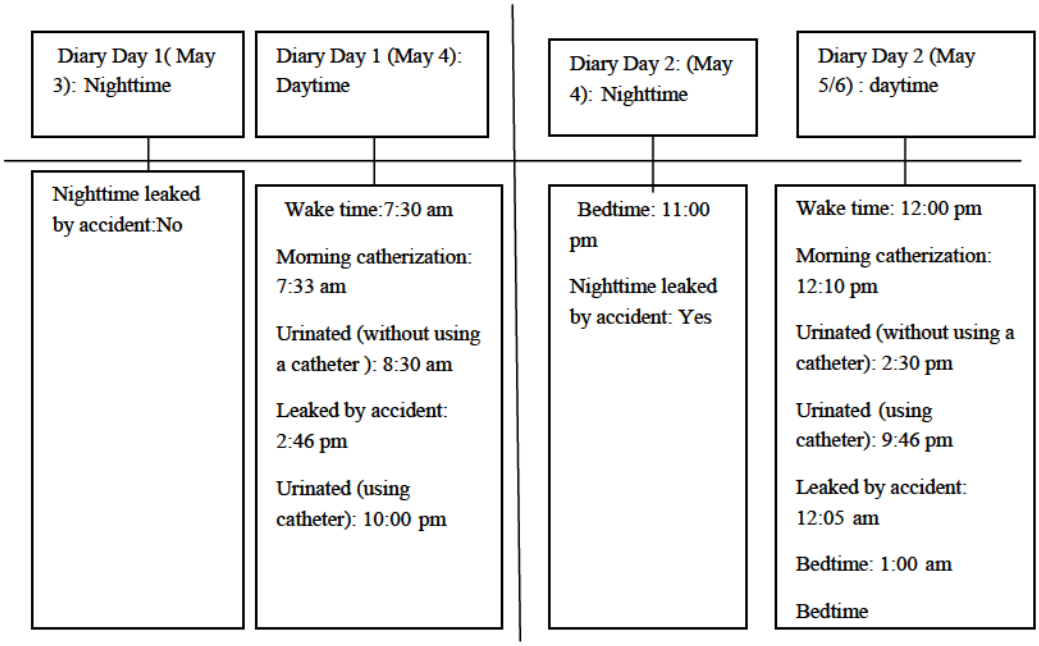
- Study baseline diary information refers to the baseline information collected at the start of study 191622-120 (see Section 2.2).
- For study baseline and post-treatment visits, analyses will be based on the diary data collected over two consecutive days. For each day, the bladder diary will be used to collect date, time, and type of voiding episode (urinary incontinence, catheterization, or voluntary void) for each daytime episode (time between waking up to start the day and going to bed to sleep for the night). Furthermore, volume of urine on catheterization at morning wakening, the time the patient went to bed to sleep at night and the time the patient woke up in the morning and presence/absence of night time urinary incontinence will be collected for each diary day.

- The visit windows defined in Section 2.2 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:

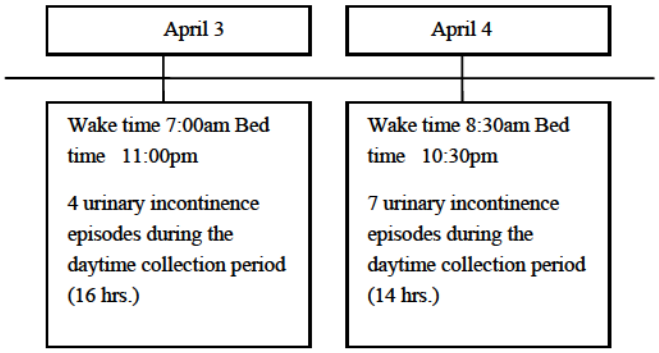
  1) Apply visit windows defined in Section 2.2, which are based on days from the date of study drug injection.

  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 diary 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 episode collected up to the time of injection will be counted towards the baseline diary data.

  3) Using the example below, the first daytime 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 two calendar days. In the data set, for a given daytime, even if the daytime period goes over two calendar dates it will be recorded under the same calendar date (i.e., if the patient goes to bed for the night after midnight). The time of the day will be used to accurately attribute the date of the event.



- If there is a missing daily average frequency of episodes of daytime urinary incontinence at study baseline, the imputed values from study 191622-120 will be utilized (see the analysis plan for study 191622-120) .
- 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 defined in Section 2.2 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

Not applicable.

3.2 Disposition and Exit Status

For study 191622-121, patient disposition table will be produced by cycle and for the study overall. The overall study disposition summary table will display summary by what the patients received in Cycle 1 (safety treatment groups in Study 191622-120) and for the

overall BOTOX-treated population. For the by cycle tables, summaries will be presented by the BOTOX treatment received in the given cycle. A listing of patients' disposition information will also be generated.

3.3 Study Duration

See Section 6.1.1.

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 and table will be produced for these significant protocol deviations. The protocol deviation table will be presented by Cycle 1 treatment groups (safety treatment groups in Study 191622-120) and for the overall BOTOX-treated group. Furthermore, the deviation listing will present the deviation type and detail.

4. Demographics and Other Baseline Characteristics

Baseline assessments are defined to be assessments taken prior to first BOTOX injection received in study 191622-120.

4.1 Demographics

Age, race, sex, weight (kg) and height (cm) will be summarized for the overall BOTOX-treated group and by Cycle 1 treatment groups. Race will be summarized as Caucasian, Black, Asian, Hispanic, and Other.

4.2 Disease Characteristics

The following baseline information will be summarized for the overall BOTOX-treated group and by Cycle 1 treatment groups:

- study baseline information on stratification factors (age < 12 vs ≥ 12 years; daytime urinary incontinence ≤ 6 vs. > 6 episodes over the 2-day diary collection period),
- 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. The number and percentage of patients that have 0, 1, 2, 3 and > 3 UTIs within 6-months of screening will also be summarized
- A patient's neurological characteristics (spinal dysraphism, spinal cord injury or transverse myelitis), 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 first BOTOX injection. Prior medications will be summarized for the overall BOTOX-treated group and by Cycle 1 treatment groups.

4.3.1 Prior Anticholinergic Medications for Urinary Incontinence

The number and percentage of participants with prior anticholinergic medications for urinary incontinence will be summarized by WHO Drug Class and WHO DDE preferred drug name.

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. The summary will be presented by treatment cycle.

4.4 Concomitant Medications/Procedures

A concomitant medication is any medication which is administered any time after the first BOTOX injection.

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 for the overall BOTOX-treatment group and by Cycle 1 treatment groups.

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 concomitant anticholinergic medication for the overall BOTOX-treatment group and by Cycle 1 treatment groups.

4.4.3 Concurrent Procedures

A patient listing of concurrent procedures will be produced. This listing will include information on the BOTOX cycle and BOTOX dose received.

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 overall BOTOX treated group and by Cycle 1 treatment groups.

5. Efficacy Analyses

All efficacy analyses will be by treatment cycle and by treatment received at each cycle, for the BOTOX treated population. The key timepoint for each efficacy variable and cycle is 6 weeks post treatment.

5.1 Collection of Key Efficacy Measurement and Derivation of Key Efficacy Variable

In this long-term extension study no primary or secondary efficacy variable has been defined. However, the key efficacy measure is the change from baseline to posttreatment 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 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 study baseline frequency is defined as the daily average frequency of episodes of daytime urinary incontinence preceding the study treatment in study 191622-120.

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 (see Section 2.3 for further details). Furthermore, if there is just 1-day 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 key time point for this change from baseline endpoint will be week 6 after each treatment/injection.

5.2 Key Efficacy Analyses

Since there is no primary efficacy measure, this section describes the analysis for the key efficacy variable.

For each cycle, for each post-treatment visit, mean values and mean change from study baseline values for the daily average frequency of normalized daytime urinary incontinence episodes will be presented together with the associated t-distribution based 95% CIs for the mean change from study baseline. This summary will be presented for each BOTOX treatment group of that cycle. This summary will also be repeated for the non-normalized daily average frequency of daytime urinary incontinence episodes. The key timepoint for analysis for each cycle is week 6 posttreatment.

For patients that increased their BOTOX dose from 50 U to 100 U or from 100 U to 200 U a paired difference will be derived between the lower dose cycle and the subsequent higher dose cycle's week 6 daily average frequencies normalized daytime urinary incontinence episodes values. These values will be summarized using mean paired difference, associated standard error and paired t-test.

5.3 Other Efficacy Analyses

In this section all the other efficacy variables and analyses are discussed.

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 a reduction from baseline in daily average frequency of normalized daytime urinary incontinence episodes of at least 50%, 75%, 90%, and 100% will be summarized within each treatment cycle, by providing the percentages and the associated 95% confidence intervals, by the treatment group for each posttreatment visit. The 95% confidence interval will be derived using the exact Clopper-Pearson confidence limits for the binomial proportions.

5.3.2 Urine Volume at First Morning Catheterization (mL)

For urine volume at first morning catheterization (mL), for each BOTOX treatment cycle, the mean study baseline, mean raw values and mean change from study baseline and associated 95% CI for the mean change from study baseline will be derived for each visit by treatment group .

5.3.3 Presence or Absence of Night Time Urinary Incontinence

For the analysis of night time urinary incontinence, for each BOTOX treatment cycle, 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. 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.

5.3.4 Duration of effect

For each treatment cycle, duration of treatment effect will be evaluated by the BOTOX treatments groups of the given cycle by assessing the following two variables.

- Time between last BOTOX injection and patient's request for the following injection (re-treatment)
- Time between last BOTOX injection and qualification for retreatment (retreatment with the next injection)

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

For each cycle, 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 retreatment will be estimated. The associated 95% CIs will also be presented for each treatment group. The proportion of patients requesting retreatment during the study will also be presented.

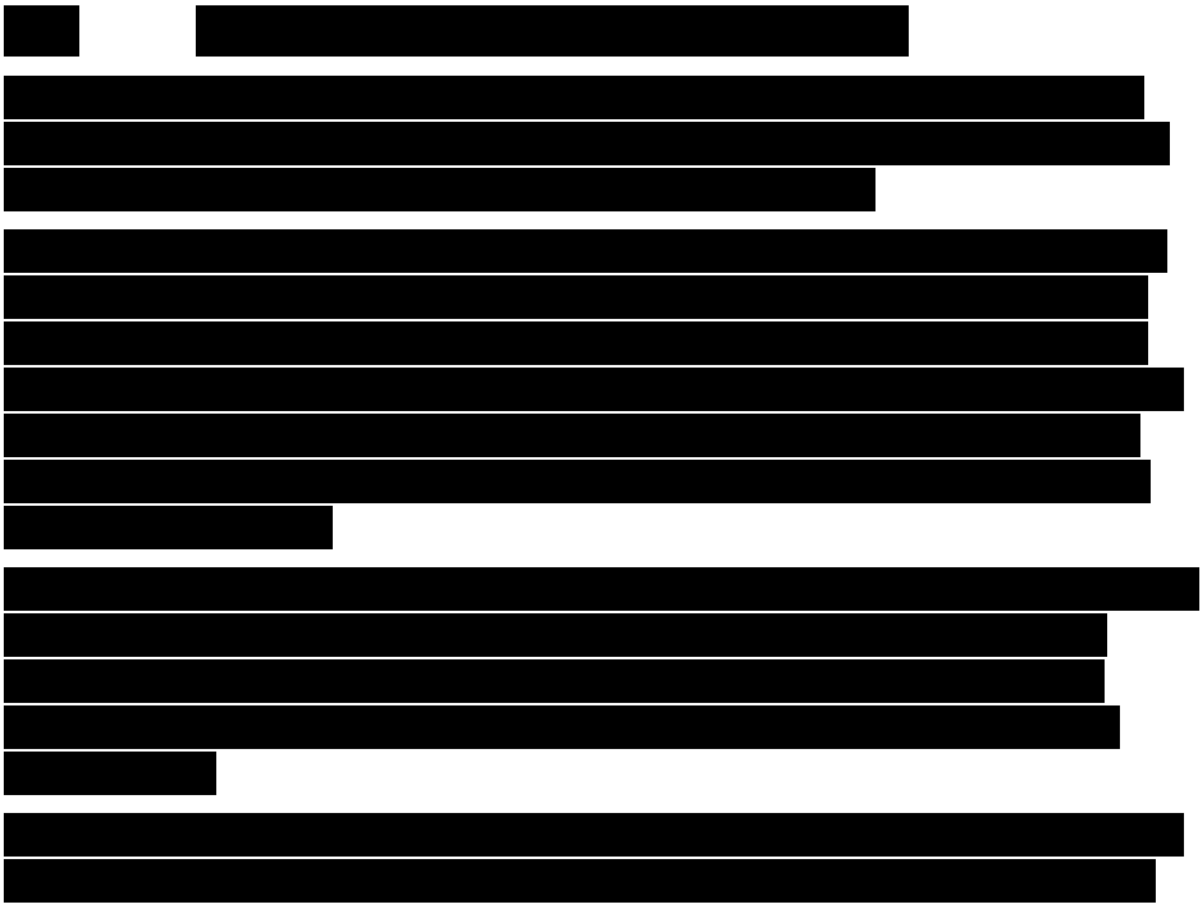
The time to qualification for retreatment will be summarized in a similar manner.

For each patient and BOTOX dose the average time to request for retreatment and the average time to qualification for retreatment will also be derived. Descriptive statistics of these derived values will be presented for each BOTOX dose.

5.3.5 Modified Treatment Benefit Scale (TBS)

The modified Treatment Benefit Scale (TBS) is single-item scale completed for each cycle at weeks 6 and 12 post-treatment, and at the qualification for retreatment visit if the patient qualifies for re-treatment.

A patient is considered to have a positive treatment response if she/he has responded to the TBS question as either "greatly improved" or "improved". For each treatment cycle, the numbers and proportions of patients with a positive treatment response will be summarized by visit (week 6 and 12) and treatment group.



[redacted]

6. Safety Analyses

Safety information includes treatment exposure, adverse events, laboratory assessments, vital signs and bladder and kidney ultrasound assessment.

6.1 Study Treatment – Exposure and Administration

6.1.1 Exposure to Study Treatment(s)

Cumulative treatment duration from Treatment 1 day 1 (study 191622-120) and cycle based treatment duration for each cycle will be derived as follows:

Cumulative treatment duration:

Cumulative duration = exit date – Treatment [1] day 1 + 1

Cycle [X] treatment duration:

If patient goes on to cycle [X+1],

Cycle [X] duration = date of Treatment [X+1] -1 – Treatment [X] day 1 + 1

= date of Treatment [X+1] – Treatment [X] day 1

If the number of BOTOX injection the patient received is [X],

Cycle [X] duration = exit date – Treatment [X] day 1 + 1

The exit day would be the exit day in study 191622-121.

A summary (mean, median and standard deviation) of the cumulative treatment duration will be presented for the overall BOTOX treated group and by Cycle 1 treatment group. Furthermore, for each cycle, the cycle treatment duration will be presented for each treatment group.

The number of patients with cumulative treatment duration of ≥ 2 weeks, ≥ 6 weeks, ≥12 weeks, ≥18 weeks, ≥24 weeks, ≥30 weeks, ≥36 weeks, ≥42 weeks, ≥48 weeks, ≥ 54 weeks, ≥ 60 weeks, ≥ 66 weeks, ≥ 72 weeks, ≥ 78 weeks, ≥84 weeks, ≥90 weeks and ≥ 96 weeks will be presented for the overall BOTOX treated population. Similar analysis table will also be generated for each cycle by treatment group.

A treatment exposure listing will also be generated. The listing will display both the cumulative and cycle duration of exposure.

6.1.2 Administration of Study Treatment(s)

For the BOTOX injections, a patient listing will be produced. The listing will present, for each patient, the time and date of all the injections, the number of injection sites and volume injected.

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 first BOTOX injection.

An AE will be considered a cycle 1 treatment-emergent adverse event (TEAE) if it fulfills one of the conditions below:

- the start date of the AE is on or after the 1st BOTOX injection and prior to the date of the 2nd BOTOX injection

- the AE started before the 1st BOTOX injection and increased in severity or became serious during the cycle (from date of 1st BOTOX injection to the day before the 2nd injection).

For subsequent cycles (cycle's number > 1) an AE is considered a TEAE in the current cycle if it fulfills one of the conditions listed below.

- the AE start date is within the cycle i.e., it is on or after the date of the cycle injection and prior to the date of the next injection
- the AE has increased in severity or became serious during the current cycle

The incidences of TEAEs will be summarized by BOTOX treatment cycle.

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.

The number and percentage of patients who have treatment-emergent serious adverse events (TESAE) will be summarized by system organ class, preferred term and treatment group. Similar summary will be presented for patients with TEAE leading to discontinuation from the study. In addition, separate patient listings will be generated for deaths, SAEs, and TEAEs leading to study discontinuation.

In addition, the incidence of TEAEs, SAEs, study drug/study injection procedure related TEAEs, deaths and TEAEs leading to study discontinuation will be reported for the overall study period.

All the summaries discussed above will be based on all AEs observed during the entire cycle. Since the design of this study allows patients to request/receive retreatment from week 12 (day 84) onward, an additional summary showing the number and percentage of patients with TEAEs by preferred term and treatment group in descending order of incidence will be presented for the TEAE observed prior to or on day 84 after each injection cycle. This will allow for a comparison across dose groups for the same duration of time (ie, since patients can request retreatment from week 12 onwards, patients remain in a cycle for varying time periods). Therefore this analysis provides a more direct comparison across dose groups.

In addition, the number and percentage of patients who have a treatment-emergent UTI during the first 2 weeks (14 days), the first 12 weeks (84 days), and during the overall treatment cycle will be presented by the treatment received in each treatment cycle.

The number of UTI events per patient year will be summarized for the six month prior to screening and for each BOTOX treatment cycle. The number of UTI events per patient year, for the BOTOX treatment cycle, is defined as follows: (The sum of all the patients UTI events)/ (The sum of all the patients duration in years during the BOTOX treatment cycle). The number of UTI events per patient year for the 6-months prior to screening is similarly defined. All patients will be included in these analyses irrespective of whether they experienced a UTI or not.

6.2.1 Potential Distant Spread of Toxin Adverse Events (applicable to BOTOX® studies only)

To assess possible distant spread of toxin (PDSOT), 39 MedDRA preferred terms that may be associated with botulinum toxin effects have been identified. All AEs associated with PDSOT will be tabulated by SOC and treatment group; in addition, all PDSOT AEs will be listed by subject. The 39 terms are listed below.

MedDRA Preferred Terms Evaluated for Possible Distant Spread of Toxin

Cardiac Disorders
- Bradycardia

Eye Disorders
- Accommodation disorder
- Diplopia
- Extra ocular muscles paresis
- Eyelid function disorder
- Eyelid ptosis
- Pupillary reflex impaired
- Vision blurred

Gastrointestinal Disorders
- Constipation
- Dry mouth
- Dysphagia
- Ileus paralytic

Infections and Infestations
- Botulism

Musculoskeletal and Connective Tissue Disorders
- Muscular weakness

Nervous System Disorders
- Bulbar palsy
- Cranial nerve palsies multiple
- Cranial nerve paralysis
- Dysarthria
- Facial paralysis
- Facial paresis
- Hyporeflexia
- Hypotonia
- Paralysis
- Paresis cranial nerve
- Peripheral nerve palsy
- Peripheral paralysis
- Speech disorder
- Vocal cord paralysis
- Vocal cord paresis

Renal and Urinary Disorders
- Urinary retention

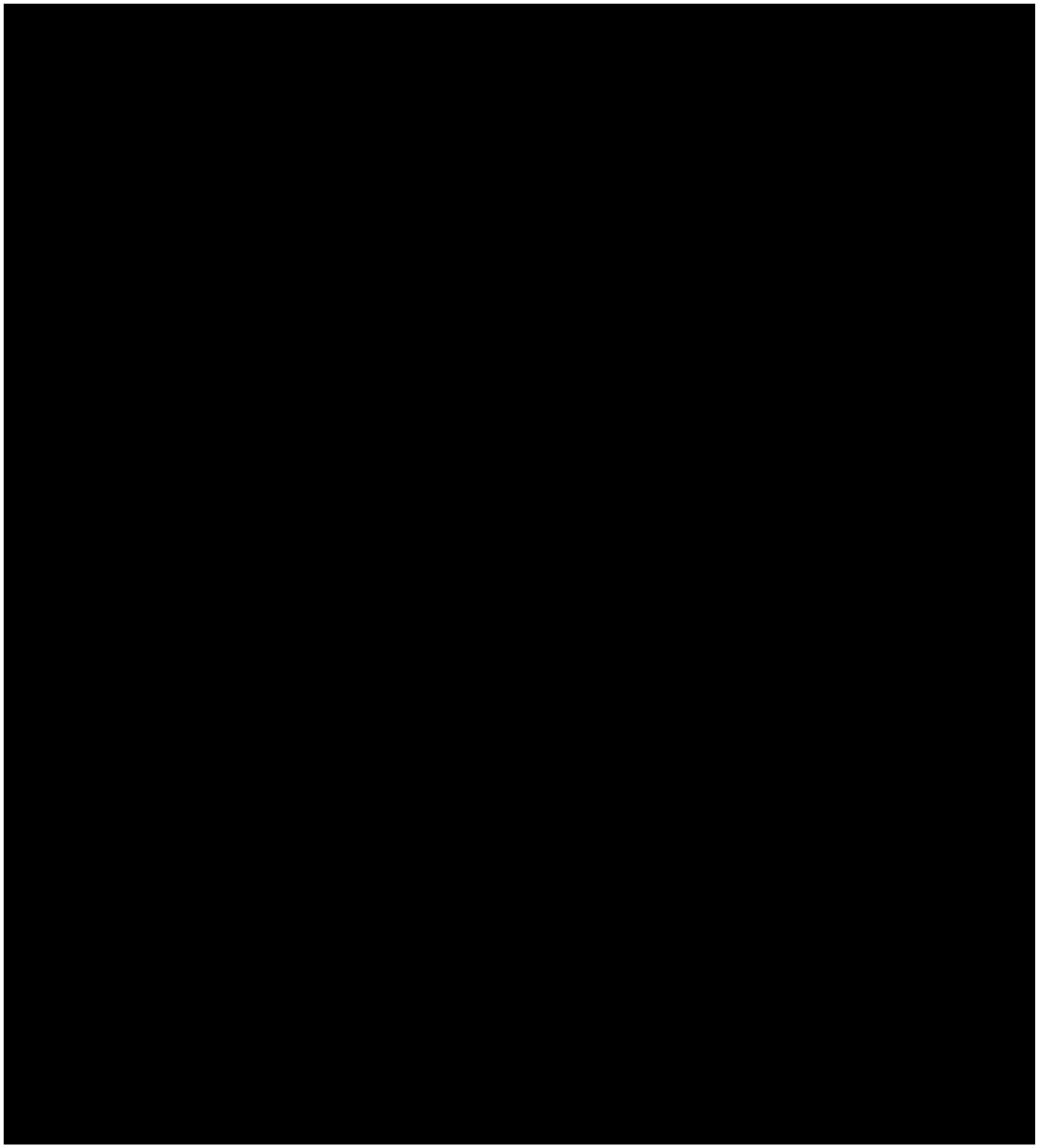
Respiratory, Thoracic and Mediastinal Disorders
- Aspiration
- Diaphragmatic paralysis
- Dysphonia
- Dyspnoea
- Pneumonia aspiration
- Respiratory arrest
- Respiratory depression
- Respiratory failure

Reproductive System and Breast Disorders
- Pelvic floor muscle weakness

Note: The evaluation of events mapping to these terms will take into consideration the known mechanism of action of BOTOX, the temporal relationship of the event (time to onset of the AE), the duration of the event, any re-challenge information if applicable, confounding factors that may include co-morbidities, past medical history, concomitant medications and other non-specific constitutional symptoms of a subject. In accordance with this, certain

term may be excluded from the consideration for PDSOT AEs. For example, since BOTOX is injected into the urinary bladder for treatment of neurogenic overactive bladder, and since urinary retention is considered an expected localized effect, the preferred term 'urinary retention' will not be considered a PDSOT event for this study.

[redacted]



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8. Health Outcomes Data Analyses

All analyses of health outcome variables are described in Section 5.

9. Interim Analyses

When all patients in study 191622-120 exit the study, there will be a data base lock (DBL) for study 191622-120 and a subsequent interim analysis for study 191622-121. A separate analysis plan is available with details of the interim analysis for study 191622-121. After this interim analysis the patients, investigator and Allergan staff will all be unblinded.

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

The number of patients that have reduction from baseline in daytime urinary incontinence episodes that meet certain threshold will not be analyzed using the non-normalized daytime rates of incontinence episodes. However, the non-normalized daily average frequency of daytime urinary incontinence episodes will be summarized.

13. References

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

14. 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.

Amendment 1

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.
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
Section 5: Efficacy Analyses	Subgroup analyses of key efficacy variable was removed	Only a subset of participants exit study 191622-120 and enroll in study 191622-121. These subgroup analyses are performed in study 191622-120
[redacted]	[redacted]	[redacted]
Section 6.2: Adverse Events	Section was re-written to reflect current company standard. For example updated definition of treatment-emergent adverse event	To reflect current company standard
Section 6.2.1: PDSOT adverse events	Paralysis flaccid was removed from the list of preferred terms. The preferred term "VII nerve paralysis" was replaced by "Facial paralysis"	Due to the update from MedDRA version 18.1 to version 19.0, Paralysis flaccid is being mapped to Paralysis, which is already included in the PDSOT list
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Sections	Revision	Rationale
Section 9: Interim Analyses	Clarification that the planned interim analyses will have a separate interim analysis plan which will be a subset of analyses in the final analysis plan.	Full tables and listings are not required for the interim analysis. Intention is to support Final CSR of study 191622-120, providing key safety/efficacy data of repeat treatments for FDA submission.

Amendment 2

Sections	Revision	Rationale
Section 2.2 Analysis Visit Windows	Deleted the following text: "For laboratory and vital signs analysis, baseline refers to study baseline, i.e. the baseline information collected at the start of study 191622-121. This will be referred to as study baseline throughout this document."	To be consistent with all other assessments collected in this study, baseline now refers to information collected at the start of study 191622-120.
Section 2.3: Data Conventions	Added the following text: "Study baseline and baseline are used interchangeably throughout this document. They both refer to the baseline information collected at the start of study 191622-120.	To clarify at the beginning of this document that baseline refers to information collected at the start of study 191622-120.

ALLERGAN

Final Analysis Plan for 191622-121 Amendment 2

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
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