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Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate an Alternative Injection Paradigm for OnabotulinumtoxinA (BOTOX®) in the Treatment of Overactive Bladder in Patients with Urinary Incontinence (LO-BOT).

Statistical Analysis Plan Date: 07 March 2019

STATISTICAL ANALYSIS PLAN

07 March 2019

Final 2.0

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate an Alternative Injection Paradigm for OnabotulinumtoxinA (BOTOX®) in the Treatment of Overactive Bladder in Patients with Urinary Incontinence

Protocol Number: CMO-US-URO-0470

Protocol Date: Amendment 1, 08 May 2018

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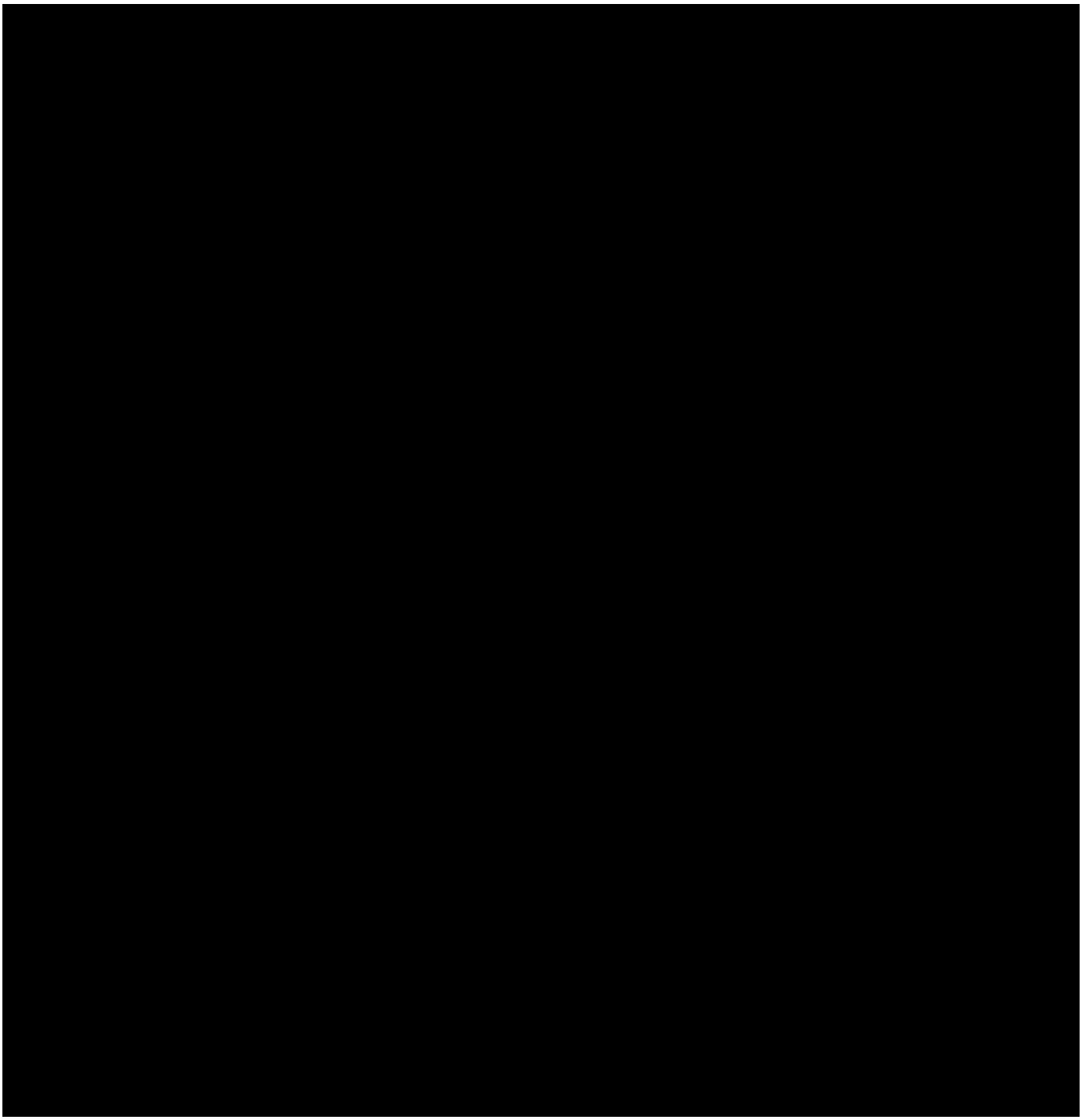

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term/Abbreviation	Definition
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BOTOX	Botulinum Toxin Type A Purified Neurotoxin Complex (US adopted name onabotulinumtoxinA), referred to as BOTOX
BMI	Body Mass Index
CI	Confidence Interval
CIC	Clean Intermittent Catheterization
CM	Concomitant Medication
CMH	Cochran Mantel-Haenszel
CSR	Clinical Study Report
DB	Double-blind
eCRF	Electronic Case Report Form
I-QOL Questionnaire	Incontinence Quality of Life Questionnaire
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
OAB	Overactive Bladder
OL	Open-label
PDSOT	Possible Distant Spread of Toxin
PVR	Post-void Residual
QOL	Quality of Life
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
PT	Preferred Term
TBS	Treatment Benefit Scale
TEAE	Treatment-emergent Adverse Event

TLG	Tables, Listings, and Graph
UTI	Urinary Tract Infection
UUI	Urgency Urinary Incontinence
WBC	White Blood Cell
WHO	World Health Organization
WHODDE	World Health Organization – Drug Dictionary Enhanced

1 Introduction

This Statistical Analysis Plan (SAP) details of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP is finalized and signed prior to any of the following: study unblinding, database hard lock, or primary analysis data cut-off to ensure lack of bias. For operational efficiency an earlier time for finalizing and signing is usually targeted, i.e., prior to primary analysis data cut-off. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

[redacted] is responsible for the statistical analysis and reporting of the study data.

Prior to database hard lock, a final review of data and Tables, Listings, and Graphs (TLGs) meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. A meeting to determine analysis set classifications may also be held prior to database hard lock.

A primary analysis is planned for the study and more details in Section 7.

1.1 Study Objectives and Design

1.1.1 Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of a single treatment of BOTOX, administered using an alternative injection paradigm, followed by a second treatment (if applicable) with BOTOX in patients with overactive bladder (OAB) with urinary incontinence whose symptoms have not been adequately managed with an anticholinergic.

Following the screening period, patients meeting the study inclusion/exclusion criteria will be randomly assigned by an interactive web response system (IWRS) to 1 of 2 treatment arms (BOTOX 100 U or placebo) in a ratio of 2:1 (Botox 100 U: Placebo). A central randomization scheme will be utilized. The overall enrollment period is estimated to be 24 months.

One randomization number will be assigned to each patient prior to the first treatment and will be associated with one of the following treatment arms:

- Double-Blind Period

  BOTOX 100 U

Placebo

- Open-Label Period

  BOTOX 100 U (DB treatment)/BOTOX 100 U (OL treatment if qualified)

  Placebo (DB treatment)/BOTOX 100 U (OL treatment if qualified)

Subjects will be eligible to receive a second treatment if all the predefined OL treatment criteria are met (see protocol Section 5.10.2). All eligible subjects will receive BOTOX 100 U for OL treatment.

Subjects will be followed regularly for safety and efficacy at post-treatment visits. Subjects will complete up to 2 treatments with a minimum study participation of 25 weeks (i.e., if subject requests a second treatment at Week 12 and qualifies for second treatment) and a maximum duration of 53 weeks (i.e., if a subject qualifies for OL treatment at Week 30, receives an injection at Week 34, and completes other study visits at the maximum allowable visit window).

1.1.2 Primary Study Objective

The primary objective of this study is to evaluate the efficacy and safety of BOTOX 100 U (onabotulinumtoxinA), compared to placebo (PBO), when injected into the bladder using an alternative injection paradigm (2 trigonal and 8 peri-trigonal injections) in reducing the number of daily urinary incontinence episodes in subjects with OAB and urinary incontinence whose symptoms have not been adequately managed with an anticholinergic.

1.1.3 Secondary Objectives

The secondary objectives of this study are to evaluate the quality of life (QOL) impact, duration of treatment effect, early onset of treatment effect, and safety of BOTOX (100 U) in subjects with OAB and urinary incontinence whose symptoms have not been adequately managed with an anticholinergic.

1.1.4 Sample Size

Sample size calculation and power consideration is discussed in Section 7.5 of the study protocol.

2 Analysis Populations and Data Conventions

2.1 Analysis Populations

2.1.1 Double-Blind Period

The enrolled subjects (including all subjects who signed informed consent) will be used for subject disposition summary.

2.1.1.1 Intent-to-treat (ITT) Population

The ITT Population will include all randomized subjects. Demographics and baseline characteristics will be analyzed using the ITT Population. Subjects will be grouped and analyzed according to their randomization assignment, regardless of the actual treatment received.

2.1.1.2 Modified Intent-to-treat (mITT) Population

The mITT Population will include all randomized subjects who had at least one efficacy assessment at the baseline and a post-baseline visit. Efficacy variables will be analyzed using the mITT Population. Subjects will be grouped and analyzed according to their randomization assignment, regardless of the actual treatment received.

2.1.1.3 Safety Population

The safety population will include all patients who receive the study drug (BOTOX 100 U or placebo). All safety variables will be analyzed using the Safety Population. Patients will be grouped and summarized according to the treatment they actually received.

2.1.2 Open-Label Period

Subjects who entered open-label re-treatment period will include subjects who are qualified for re-treatment and has an initiation of open-label (OL) BOTOX 100 U treatment.

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2.3 Data Conventions

The following are general conventions for the analysis of study data. If alternative methods are present in the specific evaluation sections of this SAP, those conventions will take precedence over these general conventions.

- For double-blind period, summaries are based on the ITT population, mITT population, or safety population (described in Section 2.1) and will be presented by treatment group (BOTOX 100 U and Placebo).

- For open-label period, summaries are based on the subjects who entered open-label re-treatment period (described in Section 2.1) and will be presented by BOTOX 100 U/ BOTOX 100 U and Placebo/BOTOX 100 U
- Continuous study measurements will be summarized by treatment group and time point (as applicable) using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Mean and median will be presented with one more decimal place than the precision of the data. Standard deviation will be presented with two more decimal places than the precision of the data. Minimum and maximum will be presented with the same precision as the original data.
- Categorical study assessments will be summarized by treatment group and time point (as applicable) using frequency counts and percentages. Percentages will be presented with one decimal place (xx.x), with the exception of 100%, which will be displayed without any decimal places.
- Statistical tests for all efficacy endpoints will be 2-sided at significance level of 0.05.
- No adjustment for the multiplicity of the endpoints will be performed.
- Unless stated otherwise, the baseline for DB period will be calculated as the last observed assessment before the DB first dose date. Baseline for OL period will be calculated as the last observed assessment before the OL first dose date. Change from baseline values will be calculated as the post-baseline value minus the respective baseline value.
- All subject data, including unscheduled assessments will be displayed in subject listings.
- Unless stated otherwise, available data from screen failures will be excluded from all tables, figures, and listings.
- Unless stated otherwise, data from all the sites will be pooled for all the analyses.
- Daily average number of episodes will be rounded to one decimal place.
- Listings will be listed by randomized or actual treatment group in DB period if applicable.

[redacted]

2.3.1 Handling of Missing Data

Imputation approaches for the efficacy endpoints are described in Section 2.3.1.1, Section 2.3.1.2 and Section 2.3.1.3.

Imputation will not be performed for safety analyses.

2.3.1.1 Handling of Missing Data for Primary Efficacy Variables

The primary efficacy endpoint is:

- Change from baseline in number of episodes of urinary incontinence at Week 12 as recorded by the subject in the 3-day bladder diary.

The following algorithms will be used for diary data conventions:

If there is no diary data (i.e., none of the 3 diary days is a valid diary day), the daily average frequency of urinary incontinence episodes will be considered as missing. A valid diary day is defined as any of the three 24-hour periods with 2 or more urinary episodes of any type. For a valid diary day, if no incontinence episodes are recorded, the number of incontinence episodes on that day will be summarized as zero. For an invalid diary day, the numbers incontinence episodes on that day will be treated as missing.

If a diary is completed for at least 1 day of diary at any particular visit, then that subject's daily average frequency of urinary incontinence episodes in a 3-day period for that given visit will be estimated by using the daily average number of urinary incontinence episodes of the available days in the 3-day diary period.

If the number of episodes of urinary incontinence at study baseline is missing, it will be imputed using the median of all non-missing values regardless of treatment group at study baseline. For each scheduled post treatment visit within the 12-week period of the DB treatment period, missing values for the efficacy variable (the change from baseline in the daily frequency of episodes of urinary incontinence) will be replaced using the last observation carried forward approach. If subjects requested and received a second treatment on or after Week 12, they are no longer in DB treatment period and the LOCF rule for DB treatment period should no longer apply to them. The LOCF rule will be applied to subjects without a second treatment of BOTOX® through 36 weeks for endpoints where data are analyzed to the end of the study.

When implemented, imputation of missing values will be performed only for subjects who receive a treatment in the pertinent treatment period. For example, only subjects receiving a second treatment will have values imputed in OL treatment period; subjects who discontinued from the study during the first treatment will not have data imputed for OL treatment period.

2.3.1.2 Handling of Missing Data for Secondary Efficacy Variables

There are 5 secondary efficacy variables as follows:

- Proportion of subjects who achieve 100% reduction in urinary incontinence episodes (complete continence) from baseline (i.e., baseline prior to DB treatment).
- Change from baseline in daily average number of micturition episodes.

- Change from baseline in daily average number of urgency episodes
- Change from baseline in daily average number of nocturia episodes.
- Proportion of subjects who have a positive treatment response on the Treatment Benefit Scale (TBS) (score of either 1 or 2, representing 'greatly improved' or 'improved', respectively) at Week 12.

The derivation of the first 4 secondary endpoints above, recorded from the 3-day bladder diary at each visit, will follow the same data convention and imputation approach as for the primary efficacy endpoint described in Section 2.3.1.1.

Missing values for TBS will not be imputed.

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2.3.2 Handling of Missing Date

As a general principle, imputation of missing dates for variables will not be done. Exceptions are for start and stop dates of AEs and concomitant medications. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

The following conventions will be used for missing adverse event dates and prior and concomitant dates.

2.3.2.1 Adverse Events Onset Date

If the AE onset date is missing in which the day, month, and year are all unknown or only the day is known, the AE onset date is set to the date of initiation of the DB treatment.

For the partial AE onset date and time,

- If the year is present and the month and day are missing or the year and day are present and the month is missing:
    - If year = year of initiation of DB treatment, then set month and day to month and day of initiation of DB treatment
    - If year < year of initiation of DB treatment, then set month and day to December 31st.
    - If year > year of initiation of DB treatment, then set month and day to January 1st.
- If the month and year are present and the day is missing:
    - If year = year of initiation of DB treatment and:
        - if month = month of initiation of DB treatment then set day to day of initiation of DB treatment
        - if month < month of initiation of DB treatment then set day to last day of month
        - if month > month of initiation of DB treatment then set day to 1st day of month
    - If year < year of initiation of DB treatment then set day to last day of month
    - If year > year of initiation of DB treatment then set day to 1st day of month
- If the imputed AE onset date is after AE stop date, then set the onset date to the AE stop date.

2.3.2.2 Prior and Concomitant Medications Date

If the start date of medication is completely missing in which the day, month, and year are all unknown or only the day is known, then the start date will not be imputed. Similar rules will be applied for the end date of medication.

- For the partial start date of medication,
    - If the year is present and the month and day are missing or the year and day are present and the month is missing, set month and day to January 1.
    - If the year and month are present and the day is missing, set day to 1st day of month.
    - If the imputed start date of medication is after the non-imputed end date of medication, then the start date will be set to the end date of medication.
- For the partial end date of medication,
    - If the year is present and the month and day are missing or the year and date are present and the month is missing, set month and day to December 31.
    - If the year and month are present and the day is missing, set day to last day of the month.

3 Disposition and Exit Status

3.1 Screening Log Data

Number of screen failures and reason for failure will be summarized.

3.2 Disposition and Exit Status

The number and percentage of subjects in each analysis population will be summarized by treatment group and overall. For the subjects who discontinued early, the primary reason for discontinuation will be summarized. Duration in DB and OL period will be calculated as below and will be summarized:

- For subjects were not re-treated, duration in DB period will be calculated as (date of discontinuation/completion– date of initiation of DB treatment + 1).
- For subjects were re-treated, duration in DB period will be calculated as (date of initiation of OL treatment – date of initiation of DB treatment + 1); duration in OL period will be calculated as (date of discontinuation/completion – date of initiation of OL treatment + 1);

Study day of discontinuation will be calculated as below and listed.

- For subjects that terminate the study early and were not re-treated, study day of discontinuation will be calculated as (date of discontinuation– date of initiation of DB treatment + 1).
- For subjects that terminate the study early and were re-treated, study day of discontinuation will be calculated as (date of discontinuation– date of initiation of OL treatment + 1).

Number and percentage of subjects randomized in each country and site will be presented by treatment group and overall.

A data listing for all subjects will display disposition characteristics, including date of initiation of the DB treatment and OL treatment if applicable, study completion status, last study day/date completed, reason(s) for non-completion, date of early termination assessment/study day of termination, and any specific comments related to non-completion.

3.3 Protocol Deviations

Protocol deviations (PDs) will be summarized by deviation type.

A data listing by treatment group, subject and time point will present details of each deviation.

4 Demographics and Other Baseline Characteristics

4.1 Demographics

Descriptive statistics for age, weight, body mass index (BMI) and height at study entry will be presented. Frequency tabulations for sex, ethnicity, age group (<65, >=65 years) and race (Caucasian, Black, Asian, American Indian or Alaskan Native, Other) and race (Caucasian and non-Caucasian) will be presented. This will be done for the ITT population by treatment group.

BMI is calculated as BMI (kg/m^2) = weight (kg) / $height^2$ (m).

4.2 Baseline Disease Characteristics

4.2.1 OAB Related Baseline Characteristics Recorded on the Electronic Case Report Form (eCRF)

OAB related baseline characteristics summarized in Table 3 and recorded on the electronic case report form (eCRF) from the Screening Visit will be summarized for the ITT population by treatment group.

Duration of the OAB symptoms in months is calculated as the number of months from onset date of OAB symptoms at diagnosis to the informed consent date at the screening.

(Date of Informed Consent - Overactive Bladder Onset date+ 1) / 30.25

Table 3: Overactive Bladder Related Baseline Characteristics from eCRF

Characteristic	Summarized as	Categories
Number of urinary tract infection (UTIs) occurring over the past 6 months	Continuous	N/A
Duration of OAB symptoms (in months)	Continuous	N/A
Post-void residual (PVR) volume (mL)	Continuous	N/A
Bladder volume (mL)	Continuous	N/A

4.2.2 Baseline Characteristics from 3-day Bladder Diary

Baseline characteristics derived from the 3-day bladder diary prior to the Randomization Visit will be summarized as continuous variable for the ITT Population with following listed characteristics in Table 4.

Table 4: Baseline Characteristics from 3-Day Bladder Diary

Characteristic	Corresponding Items in 3-Day Bladder Diary	Summarized as	Categories
Daily average number of incontinence episodes	Did you have accidental urinary leakage? as "Yes"	Continuous	N/A
Daily average number of urgency episodes	Was this episode associated with a sudden and urgent need to urinate? as "Yes"	Continuous	N/A
Daily average number of urgency urinary incontinence (UUI) episodes	Did you have accidental urinary leakage? as "Yes" + Was this episode associated with a sudden and urgent need to urinate? as "Yes"	Continuous	N/A
		Categorical	≤ 9 versus > 9
Daily average number of micturitions	Did you urinate into the toilet? as "Yes"	Continuous	N/A
Daily average number of nocturia episodes	Did this episode wake you from night sleep? as "Yes"	Continuous	N/A
Total volume voided per 24 hours	Record volume collected in 24 hr for this urinary episode	Continuous	N/A

4.3 Prior Medications

Prior medications are medications which started and ended before the initiation of DB treatment.

Previous medications are coded with World Health Organization – Drug Dictionary Enhanced (WHODDE), and will be summarized by chemical subgroup (ATC 4th level) and preferred World Health Organization (WHO) name by treatment group for the ITT population. Prior medications summary will include prior OAB medications, prior urinary tract infection (UTI) medication, and prior non-UTI medication.

Subjects taking the same medication multiple times will be counted once per medication.

4.4 Past Medical History

Medical history (other than for overactive bladder) and prior surgical procedure is coded in MedDRA, and will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment group for the ITT Population.

5 Efficacy Analyses

Statistical tests for all efficacy endpoints will be 2-sided at significance level of 0.05. No adjustment for the multiplicity of the endpoints will be performed.

The efficacy variables during the open-label period, no statistical tests will be performed for summaries of efficacy variables.

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

The primary efficacy endpoint is:

- Change from baseline in number of episodes of urinary incontinence at Week 12 as recorded by the subject in the 3-day bladder diary.

Refer to Section 2.3.1.1 for the algorithms for diary data conventions.

Change from baseline in number of episodes of urinary incontinence at Week 12 is derived as number of episodes of urinary incontinence per 24 hour at Week 12 minus number of episodes of urinary incontinence per 24 hour at Baseline.

5.2 Primary Efficacy Analyses

5.2.1 Primary Analyses of Primary Efficacy Variable(s)

Let $\mu 1$, $\mu 2$ be the true mean change from baseline at Week 12 in the daily average number of episodes of urinary incontinence for BOTOX 100 U and placebo, respectively.

The hypothesis of the primary analysis will be formulated as

H_0: $\mu 1 - \mu 2 = 0$ vs

H_a: $\mu 1 - \mu 2 \neq 0$.

The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model with treatment as a factor at 2 levels, and the number of UUI episodes reported at baseline (≤ 9 versus > 9 daily episodes, during the 3-day bladder diary at baseline) and baseline daily average number of episodes of incontinence as covariates. Least squares (LS) mean for each treatment group and 95% confidence interval (CI) will be calculated.

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[redacted]

[redacted]

5.3 Secondary Efficacy Analyses

5.3.1 Proportion of Subjects who Achieved 100% Reduction in Urinary Incontinence Episodes from Baseline

Subject who achieves 100% reduction in urinary incontinence episodes (complete continence) from baseline is defined as:

- If post-treatment urinary incontinence episodes = 0, set the 100% reduction in urinary incontinence episodes indicator equal to Y.
- If post-treatment urinary incontinence episodes > 0, set the 100% reduction in urinary incontinence episodes indicator equal to N.

This indicator will be derived for Week 1, Week 2, Week 6, Week 12, Week 24, and Week 30, respectively.

This endpoint will be analyzed using a Cochran Mantel-Haenszel (CMH) test adjusting for the number of UUI episodes reported at baseline (≤ 9 versus > 9 daily episodes, during the 3-day bladder diary at baseline) at each scheduled visit. Odds ratio and 95% CI (BOTOX/placebo) will be calculated.

5.3.2 Change from Baseline in Daily Average Number of Micturition Episodes

This endpoint will be analyzed at each scheduled visit (Week 1, Week 2, Week 6, Week 12, Week 24, and Week 30) using an ANCOVA model with treatment as a factor and baseline value corresponding to the given endpoint and the number of UUI episodes reported at baseline (≤ 9 versus > 9 daily episodes, during the 3-day bladder diary at baseline) as covariates. A 95% CI for the least-squares mean difference of a given endpoint between the two treatment groups will be calculated.

5.3.3 Change from Baseline in Daily Average Number of Urgency Episodes

Change from baseline in daily average number of urgency episodes at Week 1, Week 2, Week 6, Week 12, Week 24, and Week 30 will be analyzed following the same algorithm as described in Section 5.3.2.

5.3.4 Change from Baseline in Daily Average Number of Nocturia Episodes

Change from baseline in daily average number of nocturia episodes at Week 1, Week 2, Week 6, Week 12, Week 24, and Week 30 will be analyzed following the same algorithm as described in Section 5.3.2.

5.3.5 Proportion of subjects who have a positive treatment response on the Treatment Benefit Scale (TBS)

Treatment Benefit Scale (TBS) is a single-item 4-point scale is used to assess the subject-reported benefit of treatment of OAB with respect to improvement or worsening of their condition at Week 12. Responses will be summarized descriptively by treatment groups.

1- greatly improved

2- improved

3- not changed

4- worsened

TBS responders defined as subjects who rated their perception of response to treatment as either ‘greatly improved’ or ‘improved’ at Week 12 compared to baseline. This indicator will be derived for Week 12. The analysis will follow the same algorithm as described in Section 5.3.1.

5.5.2 Analysis for Continuous Endpoints

Analysis for continuous endpoints at each visit will be conducted using the similar ANCOVA models as stated in Section 5.3.2 except for change from baseline in daily UUI episodes. For change from baseline in daily UUI episodes analysis, number of UUI episodes reported at baseline (≤ 9 versus > 9 daily episodes) will be excluded from the model.

A paired t-test will be performed for the comparison between baseline and a post-treatment value at each visit for each endpoint. This analysis will follow the same algorithm as described in Section 5.4.

5.5.3 Analysis of Categorical Endpoints

Analysis for categorical endpoints at each visit will be conducted using CMH test in Section 5.3.1. Point estimate and 95% CI for the odds ratio will be calculated for each endpoint at each visit.

5.5.4 Analysis of Time to Request of Re-Treatment

The time-to-request of re-treatment between the two treatments will be analyzed using the log-rank test. Kaplan-Meier estimates of the time-to-request of re-treatment will be provided. A 95% CI for the median time-to-request of re-treatment for each treatment will be calculated.

6 Safety Analyses

All safety analyses will be conducted on the safety population. No inferential comparison between treatment groups will be performed for the safety analysis.

6.1 Exposure to Study Treatment(s)

The study drug administration will be summarized by treatment group with descriptive statistics, including cystoscope type (Flexible, Rigid), number of injection site, total volume injected. The summary will be done for double-blind and open-label period separately.

Details pertaining to the administration of study drug will be listed, including use of anesthesia, cystoscope type, date/time of injection, number of injection site, total volume injected, location of injections, etc.

Prophylactic antibiotics are to be administered beginning 1 to 3 days before study treatment, on the day of study treatment, and continuing for 1 to 3 days after study treatment. The investigator is to prescribe the appropriate antibiotic and number of days pretreatment and post treatment based on clinical judgment and local site practice. Details of prophylactic antibiotics will be listed. Treatment period for prophylactic antibiotics will be derived using the similar logic as for concomitant medication. Please refer to Table 6 for the detailed classification.

6.2 Concomitant Medications

Concomitant medications are medications which that started before initiation of DB treatment and continued into DB treatment or started after the initiation of the DB treatment. For re-treated subjects, the concomitant medications started before the initiation of OL treatment will be assigned to double-blind period. The concomitant medications started before the initiation of OL treatment and continued into OL treatment or started on or after the initiation of the OL treatment will be assigned to open-label period. Please refer to Table 6 for the detailed classification.

Concomitant medications are coded with WHODDE, and will be summarized by chemical subgroup (ATC 4th level) and preferred WHO name by treatment group for the Safety Population. Summary for concomitant medications will be based on safety population for those concomitant medications assigned to double-blind period and subjects who entered open-label re-treatment period for those concomitant medications assigned to open-label period.

Subjects taking the same medication multiple times will be counted once per medication. A medication that can be classified into several chemical subgroups is presented in all chemical therapeutic subgroups.

Table 6: Classification of Concomitant Medications (CMs) by Treatment Period

Subjects not re-treated:

Medication Start Date	Medication Stop Date	Medication Classification
CM start date < DB Treatment start date	CM stop date >= DB Treatment start date OR ongoing	DB period
CM start date >= DB Treatment start date		DB period

Subjects re-treated:

Medication Start Date	Medication Stop Date	Medication Classification
CM start date < OL Treatment start date	CM stop date >=OL Treatment start date OR ongoing	OL period
CM start date >= OL Treatment start date		OL period
CM start date < OL Treatment start date	CM stop date >= DB Treatment start date and CM stop date < OL Treatment start date	DB period
CM start date < OL Treatment start date	CM stop date >= OL Treatment start date	DB period, OL Period
CM start date < OL Treatment start date	Ongoing	DB period, OL Period
CM start date >= DB Treatment start date	CM stop date < OL Treatment start date	DB period
CM start date >= DB Treatment start date	CM stop date >= OL Treatment start date	DB period, OL Period
CM start date >= DB Treatment start date	Ongoing	DB period, OL Period

6.3 Concomitant Procedures

Concomitant procedures (including catheterization with associated frequency and reason for catheterization) will be listed. Concomitant procedures will be coded in Medical Dictionary for Regulatory Activities (MedDRA, Version 19.0 or later).

Treatment period for concomitant procedure will be derived using the similar logic as for concomitant medication. Please refer to Table 6 for the detailed classification. Concomitant procedures will be summarized.

[redacted]

6.5 Adverse Events

Treatment-Emergent Adverse Events (TEAEs) are defined as those that begin on or after initiation of first dose of study treatment. For re-treated subjects, the TEAEs started on or after the initiation of DB treatment and before the initiation of OL treatment will be assigned to double-blind period. The TEAEs started on or after the initiation of OL treatment will be assigned to open-label period. Refer to Table 7 for the classification of TEAEs by treatment period as:

- Double-blind period
- Open-label period

Table 7: Classification of TEAEs

Subjects not re-treated:

TEAE Start Date/Time	TEAE Classification
DB Treatment start date/time <= AE start date/time	Double-Blind period

Subjects re-treated:

TEAE Start Date/Time	TEAE Classification
DB Treatment start date/time <= AE start date/time < OL Treatment start date/time	Double-Blind period
AE start date/time >= OL Treatment start date/time	Open-Label period

Adverse events will be classified by type, incidence, severity, and causality. The overall incidence of AEs will be summarized using the MedDRA coding system and classified by SOC, PT, and treatment group.

An overall summary table will present the number of events and the incidence of subjects having at least one event in the following categories:

- TEAEs
- TEAEs indicated as serious (SAEs)
- TEAEs leading to study discontinuation
- TEAEs leading to death
- TEAEs related to study drug
- Serious TEAEs related to study drug
- Possible distant spread of toxin (PDSOT) TEAEs (refer to Section 6.5.2)
- TEAEs of urinary retention (Refer to Section 6.5.1)
- TEAEs of residual urine volume (Refer to Section 6.5.1)
- TEAEs of urinary tract infection (Refer to Section 6.5.1)
    - TEAEs of asymptomatic urinary tract infection
    - TEAEs of symptomatic urinary tract infection

Tabulation (using counts and percentages) of TEAEs classified by SOC and PT will be provided. In addition, Tabulation of TEAEs classified by SOC and PT will be provided for each of the following:

- Serious TEAEs
- Treatment-Related Serious TEAEs
- TEAEs leading to study discontinuation
- Treatment-related TEAEs leading to study discontinuation

Tabulation of TEAEs classified by PT will be provided for each of the following:

- TEAEs
- Serious TEAEs
- TEAEs by maximum severity
    - Subjects with multiple TEAEs with the same PT will be summarized at the maximum severity and counted one time for that PT.
- TEAEs related to study drug
- TEAEs leading to death

When reporting the number of TEAEs, if the same TEAE occurs for a subject on multiple occasions the event will be counted once for each occurrence.

All adverse events and related details will be listed by treatment group and subject. Non-treatment-emergent events will be identified in all listings, but not included in summaries.

6.5.1 Study-specific Definitions for Particular Adverse Events

All particular AEs (AE of urinary retention, AE of residual urine volume, and AE associated with possible distant spread of toxin (PDSOT)) and treatment-related particular AEs will be tabulated by SOC and PT; in addition, all particular AEs will be listed by treatment group and subject.

6.5.1.1 Definition of Adverse Event of Urinary Retention:

An adverse event of urinary retention should only be recorded when a subject has a raised PVR urine volume that requires intervention with CIC according to the following criteria:

- Subject has a PVR urine volume of ≥ 350 mL (regardless of symptoms), OR
- Subject has a PVR urine volume ≥ 200 mL and < 350 mL and the subject reports associated symptoms i.e., voiding difficulties, sensation of bladder fullness that in the investigator's opinion require CIC.

6.5.1.2 Definition of Adverse Event of Residual Urine Volume:

An adverse event of residual urine volume should be recorded if, in the investigator's opinion, the raised PVR urine volume is clinically significant but does not fulfill the above definition for urinary retention.

6.5.1.3 Definition of Adverse Event of Urinary Tract Infection:

An adverse event of UTI will be recorded if both the following criteria are fulfilled, regardless of subject symptoms:

- A positive urine culture result with a bacteriuria count of > 10^5 colony forming units/mL
- Leukocyturia of > 5/high-power field

If a subject meets the criteria for the definition of a UTI, the investigator will record whether the UTI was "symptomatic" or "asymptomatic" on the adverse event eCRF

6.5.2 Potential Distant Spread of Toxin Adverse Events

To assess possible distant spread of toxin (PDSOT), 40 MedDRA preferred terms that may be associated with botulinum toxin effects have been identified in Table 8. All AEs associated with PDSOT will be tabulated by SOC and PT; in addition, all PDSOT AEs will be listed by treatment group and subject. The 40 terms are listed below.

Table 8: MedDRA Preferred Terms for Possible Distant Spread of Toxin

Cardiac Disorders Bradycardia **Eye Disorders** Accommodation disorder Diplopia Extraocular muscle 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 VIIth nerve paralysis Facial paresis Hyporeflexia Hypotonia Paralysis Paralysis flaccid 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

6.6 Serious Adverse Events

The number and percent of subjects with serious adverse events will be tabulated by MedDRA system organ class and preferred term. In addition, a listing will be generated of subjects with serious adverse events.

6.7 Clinical Laboratory Evaluations

Urinalysis will be performed at all study visits (excluding clinic visit at Week 24) by a central laboratory; a urine culture and sensitivity test will also be performed when central laboratory

urine results are suggestive of a UTI (positive leukocyte esterase, nitrites, blood and/or microscopic sediments such as white blood cells [WBCs], red blood cells [RBCs] and/or bacteria).

For quantitative urinalysis results, actual values and changes from baseline will be summarized for each time point by treatment groups. Categorical urinalysis results will also be summarized.

Urinalysis results will be classified as low, normal, or high at each visit according to the laboratory supplied reference ranges. Shift tables of reference range changes from Baseline to each visit will be summarized.

At screening, prior to DB treatment, blood samples will be drawn from all subjects for analysis of the following laboratory tests to be performed by the central laboratory: complete blood count, creatinine, and blood urea nitrogen. All male subjects will undergo a prostate-specific antigen test also performed by the central laboratory.

All laboratory results will be listed by treatment group, subject and time point. Listings of pregnancy testing, urine dipstick testing, and urine culture sensitivity assessment will be provided separately.

6.8 Vital Signs

Collected vital signs will include pulse rate, blood pressure, and temperature.

Results for each vital sign parameter will be listed by treatment group, subject, and time point. Actual values and changes from baseline will be summarized for each time point by treatment groups.

6.9 Post-void residual (PVR) urine volume

PVR urine volume will be summarized descriptively for each treatment by visit. Change from baseline in PVR urine volume will be summarized.

6.10 Other Safety Analyses

6.10.1 Physical Examination

Physical examination results will be listed by treatment group, subject, and time point.

7 Primary Analysis

A primary analysis will occur when all patients have completed 12 weeks following double-blind period or early terminated. Only tables will be produced (no patient listings will be

produced), thus maintaining patient and site/investigator treatment blinding. The primary analysis (topline data) will be a subset of the final analyses performed for the final CSR. Analyses included in the primary analysis will be flagged in the table, figure, and listing mocks.

The main purpose of the primary analysis is for presentation of the key data as soon as possible at an international urological or urogynecological conference to ensure dissemination of results in a timely manner. The topline primary analysis data will include key efficacy and safety analysis from the first 12 weeks after double-blind treatment.

For the purpose of the primary analysis, statistics and programming staff from the vendor CRO, will have blinded and unblinded teams set up for the analysis, per details contained in the SAP and/or other documentation listing those who will be unblinded. Unblinded statistical team will work in a restricted secure study location. Responsibilities of each team are listed in Section 7.1 and 7.2.

Only Allergan study team members and corresponding co-authors will receive the topline primary analysis data (no analysis datasets and listings will be distributed, therefore the Allergan team and co-authors will not be unblinded to patient level data). Those who will be unblinded in Allergan will be listed in another document. No CSR will be authored following the primary analysis.

Full unblinding will occur following the final database lock at the end of the study, for the final CSR.

7.1 [redacted] Blinded Statistical Team

The responsibilities of the blinded statistical team are as follows:

- Compile, generate, and review of all blinded TFLs and other reports as required by the primary analysis.
- Secure provision of codes for blinded tables and listings to the unblinded statistical team, who will provide unblinded tables and listings to Allergan unblinded statistician.

7.2 [redacted] Unblinded Statistical Team

The responsibilities of the unblinded statistical team are as follows:

- Compile, generate, and review all unblinded TFLs as required by the primary analysis
- Distribute all appropriate primary analysis materials to Allergan statistician via the secure email as password protected zip files.

8 Changes from Protocol-Specified Analyses

No change from protocol-specified analysis.

9 Reference

Patrick DL, Martin ML, Bushnell DM, Yalcin I, Wagner TH, Buesching DP. Quality of life of women with urinary incontinence: further development of the incontinence quality of life instrument (I-QOL). Urology. 1999;53:71-76.

Patrick D, Khalaf K, Dmochowski R, Kowalski JW, Globe DR. Psychometric performance of the incontinence quality-of-life questionnaire among subjects with overactive bladder and urinary incontinence. Clin Ther. 2013;35(6):836-845.

10 Amendment(s)

Version Number/ Date	Comments	Rationale
2.0 / 07Mar2019	1. Updated typo to specify that efficacy output uses the mITT population instead of ITT population.	1. Protocol amendment 1 (finalized prior to the primary analysis) specified to use mITT population for all efficacy analyses. SAP 1.0 has a typo specifying efficacy analyses will use the ITT population. This was changed to mITT to be consistent with protocol amendment 1.
	2. Updated to remove 97.5% confidence intervals for the primary analysis of primary efficacy variables.	2. Protocol amendment 1 only specifies that a 95% confidence interval will be provided for the primary analysis of efficacy variables. SAP 1.0 included a 97.5% confidence interval that was not included in protocol amendment 1, so this was removed.
	3. Specified that CIC must be of duration greater than 1 day to be included in summary tables.	3. The CIC duration was updated, so the CIC summaries will be consistent with the analysis performed in Phase III trials used for drug labeling.
	4. Updated a typo where "IA" was used instead of "primary analysis"	4. There was no interim analysis on this study. Using "IA" was a typo and should have referred to the primary analysis.
	5. Other cosmetic updates	5. Cosmetic updates include the following: section references that were incorrect were fixed, a sentence that was not capitalized was corrected, and text was made subscript where appropriate.