NCT03320850

Study ID: 1839-201-021

Title: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Single-treatment, 2-stage, Dose-finding Study Evaluating the Efficacy and Safety of BOTOX® Intravesical Instillation in Participants With Overactive Bladder and Urinary Incontinence

Statistical Analysis Plan Amendment 1 Date: 07Mar 2019

1.0 TITLE PAGE

Protocol 1839-201-021

A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-controlled, Single-treatment, 2-stage, Dose-finding Study Evaluating the Efficacy and Safety of BOTOX® Intravesical Instillation in Participants with Overactive Bladder and Urinary Incontinence

STATISTICAL ANALYSIS PLAN for Stage 1- Clinical Study Report

Final: 05 Jan 2018
Amendment 1: 07 Mar 2019

2.0 TABLE OF CONTENTS

List of Tables

List of Figures

3.0 LIST OF ABBREVIATIONS

Table 3-1 List of Abbreviations

Abbreviation/Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CFB	change from baseline
CIC	clean intermittent catheterization
CSR	clinical study report
eCRF	electronic case report form
ECG	electrocardiogram, electrocardiographic
IP	investigational product
IPIS	Instillation Procedure Impression Scale
IWRS	interactive web response system
kg	kilogram(s)
KM	Kaplan-Meier
m	meter(s)
MedDRA	Medication Dictionary for Regulatory Activities
mg	milligrams
PCS	potentially clinically significant
PID	participant identification
PK	pharmacokinetic
PO	primary objective
PSA	prostate-specific antigen
PVR	post-void residual
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SD	standard deviation
SE	standard error
SI	Le Système International d'Unités (International System of Units)
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
UIE	urinary incontinence episode
ULN	upper limit of normal
UTI	urinary tract infection
UUE	urinary urgency episode
UUIE	urinary urgency incontinence episode
WHO	World Health Organization

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data specified in the final protocol of Study 1839-201-021 (version dated 08 June 2017) and the most recent amendment (amendment 2 dated 20 Dec 2018). Specifications of tables, figures, and data listings are contained in a separate document. There are two stages in this study. This SAP is for Stage 1 of the study. The SAP for Stage 2 of the study will be prepared in a separate document.

For participants with overactive bladder (OAB) and urinary incontinence who are inadequately managed by pharmacologic therapies, or are not suitable candidates for more invasive therapies, there is an unmet medical need for a less invasive, more convenient OAB treatment option. Study 1839-201-021 will investigate the efficacy and safety of BOTOX administered via intravesical instillation which will eliminate the need for cystoscopy to administer the treatment, as well as eliminate the need for prophylactic antibiotic use, and for local anesthesia of the bladder prior to administration.

This study is a multicenter, randomized, double-blind, placebo-controlled, single-treatment, 2-stage, dose-finding study. The 2-stage study design allows for an assessment of safety during Stage 1 in a conservative, placebo-controlled dose-escalating manner prior to the initiation of Stage 2 where the efficacy and safety of BOTOX instillation will be evaluated in a placebo-controlled, parallel group, dose-finding design.

Unless otherwise stated, all discussion below will be based on the Stage 1 design.

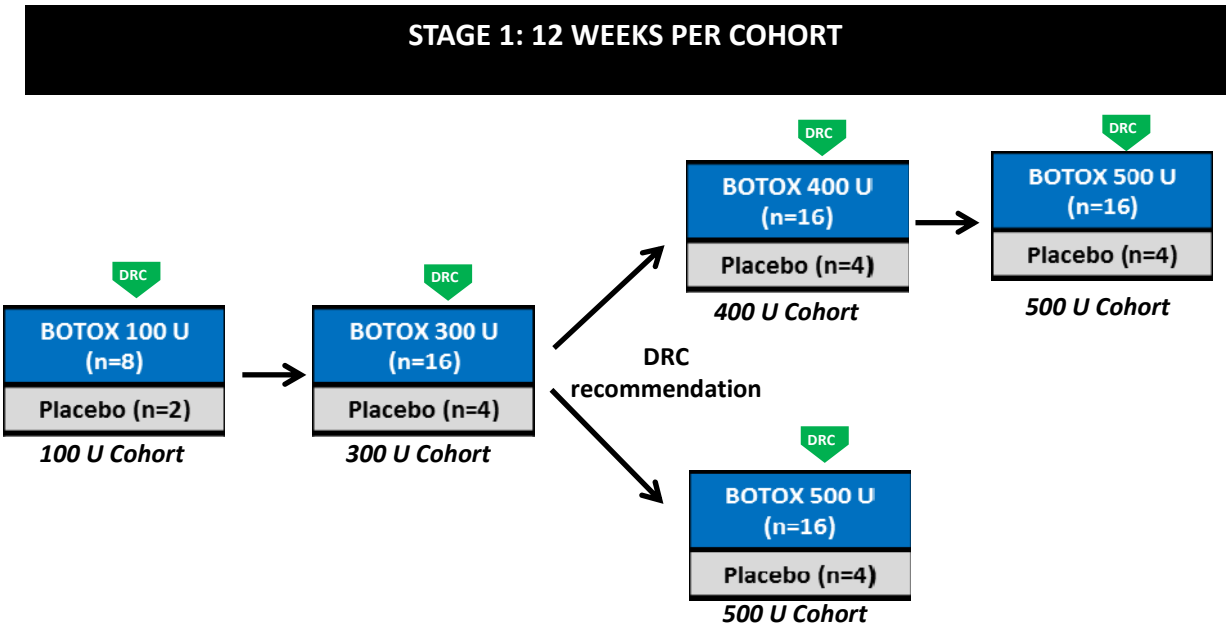
BOTOX (or placebo) intravesical instillation doses (100 U, 300 U, [400 U], 500 U) will be investigated in 3 or 4 consecutive cohorts (Figure 4-1). Upon completion of the Week 6 post instillation follow-up timepoint, unblinded safety data from each cohort will be reviewed by an independent data review committee (DRC) prior to starting enrollment into the next dose cohort. Based on the observed safety data from the 100 U and 300 U Cohorts, the DRC will recommend to proceed with either BOTOX 400 U followed by BOTOX 500 U or whether it is safe to dose escalate directly to BOTOX 500 U. If additional safety data are required by the DRC prior to proceeding with dose escalation from one cohort (or stage) to the next, additional participants may be enrolled into a cohort as recommended by the DRC.

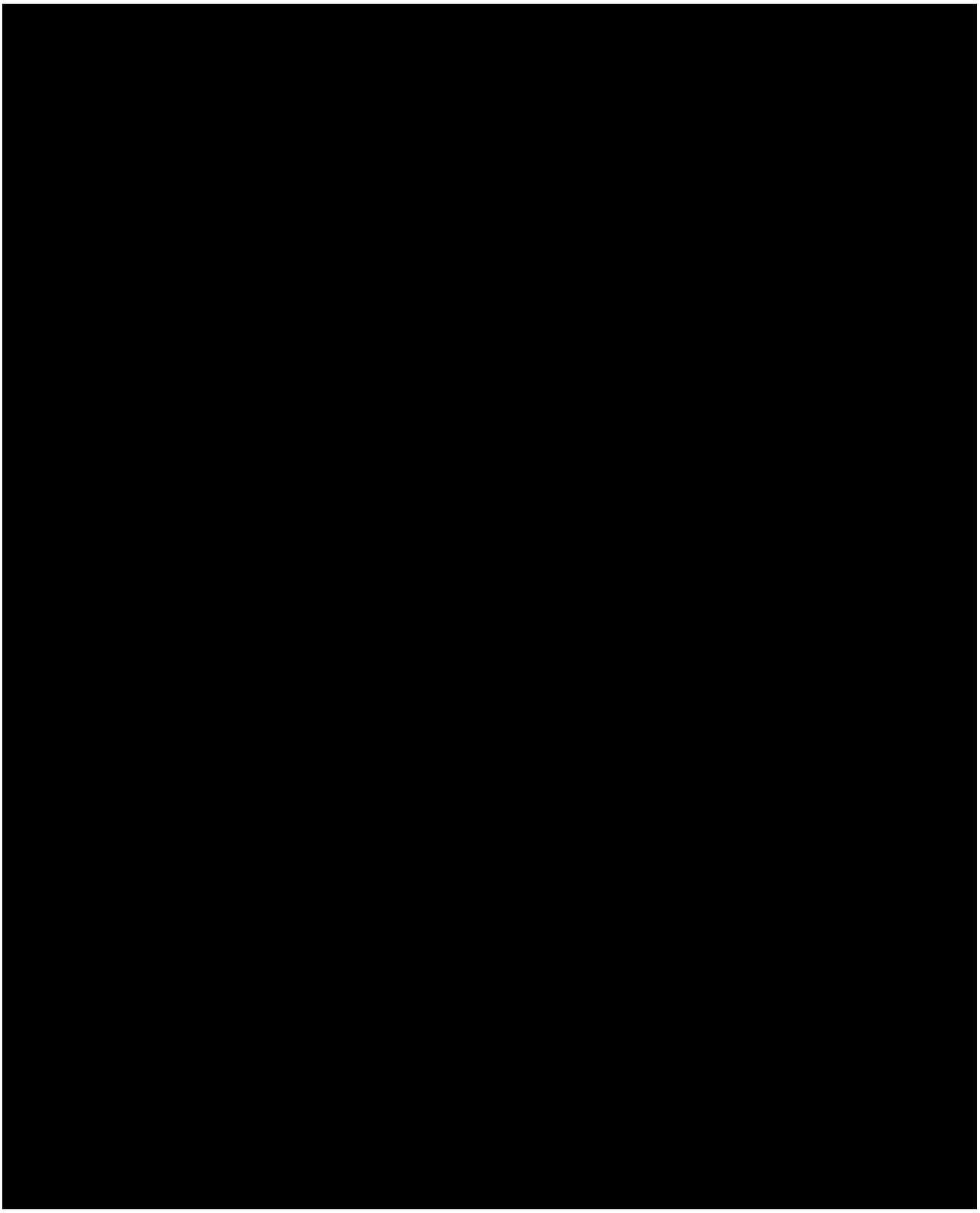
Within each cohort, participants will be randomized in a 4:1 ratio to receive either BOTOX or placebo. A total of 50 to 70 participants will be randomized to receive study treatment in Stage 1 (Figure 4-1).

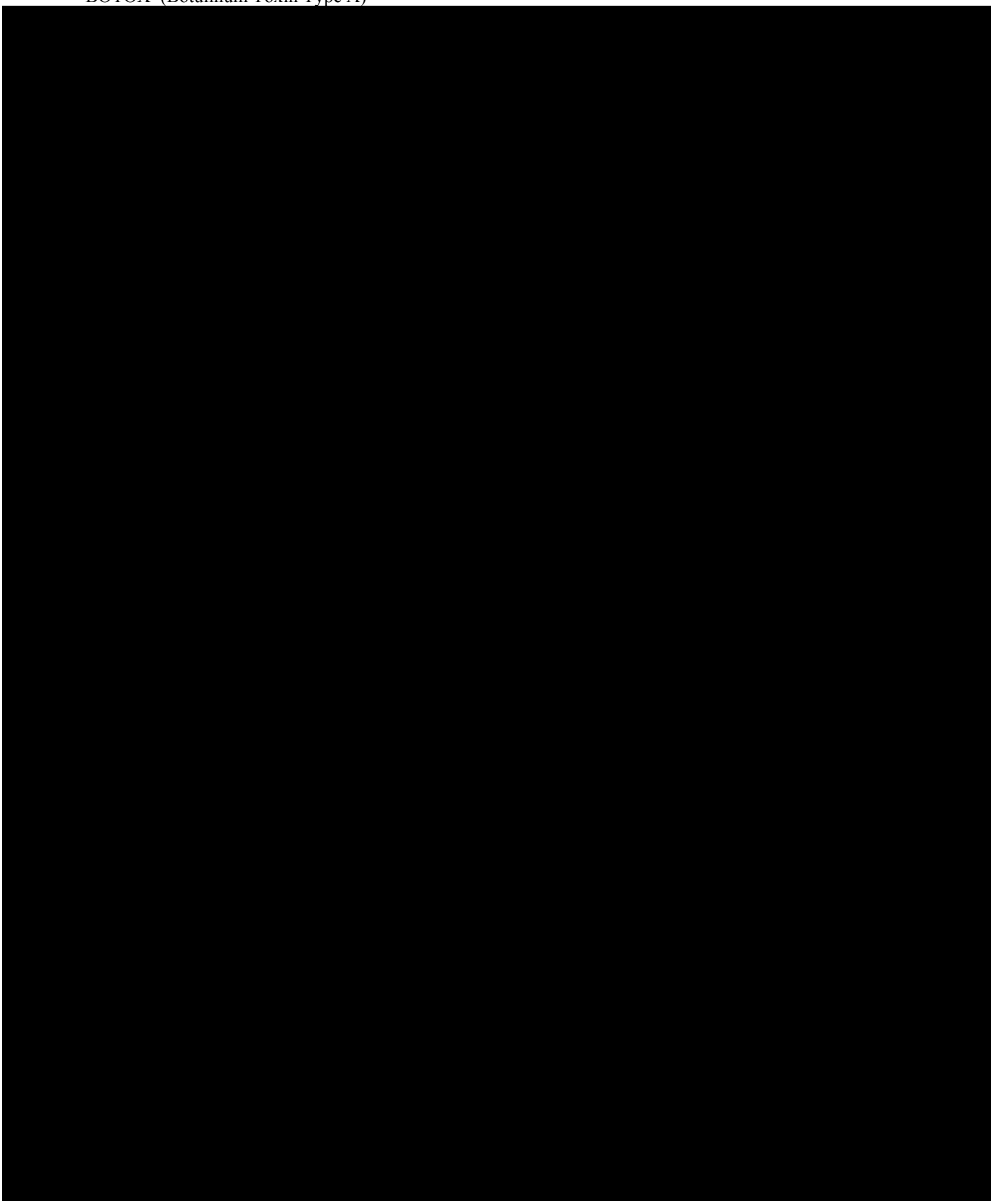
The analyses will consider up to 5 treatment groups, BOTOX 100 U, 300 U, 400 U, 500 U, and Placebo. In all analyses, data from the Placebo treatment group will be pooled across all cohorts in Stage 1 of the study.

The total duration of each participant's planned participation is 14 weeks, including a 2-week screening and 12-week treatment/follow-up period. The screening period can be extended by an additional 2 weeks in cases where a participant has a positive urine dipstick at the scheduled Day 1 visit. The schedule of activities is presented in Table 4-1.

Figure 4-1 **Schematic of Stage 1 Study Design**







5.0 OBJECTIVES

The objective of Stage 1 of this study is to compare the safety of a single treatment of BOTOX intravesical instillation, with possible doses ranging from 100 U up to 500 U, with placebo in participants with OAB and urinary incontinence. A limited exploratory analysis is also being performed on select efficacy endpoints.

6.0 ANALYSIS POPULATIONS

The Screened Population will consist of all screened participants who sign informed consent.

The Enrolled Population will consist of all participants who signed informed consent and screened with eligibility verified.

The Intent-to-Treat (ITT) Population will consist of all randomized participants. All efficacy data will be analyzed as randomized using the ITT Population.

The Safety Population will consist of all participants enrolled in this study who received the study treatment. All safety data will be analyzed as treated using the Safety Population.

7.0 PARTICIPANT DISPOSITION

The number and percentage of participants in the study populations (Safety and ITT) will be summarized by treatment group; the overall number of participants screened and enrolled will also be presented.

The number and percentage of participants who complete the study and who prematurely discontinue the study will be presented for each treatment group and pooled across treatment groups for the Safety Population. The reasons for premature discontinuation from the study as recorded on the termination pages of the electronic case report forms will be summarized (number and percentage) by treatment group for the Safety Population. All participants who prematurely discontinue during the study will be listed by discontinuation reason for the Safety Population.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Since the focus of Stage 1 of this study is on safety, all summaries in Sections 8.x will be performed on the Safety population. All continuous variables will be summarized by number of participants and mean, SD, first quartile, median, minimum, third quartile, and maximum values. Categorical variables will be summarized by number and percentage of participants.

8.1 DEMOGRAPHICS

Demographic parameters (age; age group; race; ethnicity; sex) and baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])^2 will be summarized descriptively by treatment group and overall (i.e. pooled across all treatment groups).

8.2 BASELINE DISEASE CHARACTERISTICS

The following baseline disease characteristics will be summarized descriptively by treatment group and overall for the Safety population: duration of OAB (in years), average number of UIE, UUIE, UUE, micturition episodes & nocturia episodes per day, volume voided per micturition and PVR urine volume.

8.3 PAST MEDICAL AND SURGICAL HISTORY

Medical and surgical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants with medical and surgical histories in each system organ class and preferred term will be broken out by whether they were ongoing at screening and then summarized by treatment group and overall.

8.4 PRIOR AND CONCOMITANT MEDICATIONS

Prior medication is defined as any medication taken before the date of the first dose of study treatment. Concomitant medication encompass all medicinal products that the participant was taking prior to the first dose of study treatment and which are ongoing at this visit in addition to all medications taken on or after the date of the first dose of study treatment.

Both prior and concomitant medications will be coded using the Anatomical-Therapeutic-Chemical classification text from World Health Organization (WHO) Drug Dictionary. The use of prior and concomitant medications will be summarized by the number and percentage of participants in each treatment group and overall. A separate summary table will be presented for previous pharmacotherapy for OAB (see section 8.5). If a participant took a specific medication multiple times or took multiple medications within a specific therapeutic class, that participant would be counted only once for the coded drug name or therapeutic class.

8.5 PREVIOUS PHARMACOTHERAPY FOR OVERACTIVE BLADDER

Previous pharmacotherapy for OAB are medications that were taken before the first study drug (BOTOX or placebo + Hydrogel admixture) instillation. Information on these is captured in the correspondingly named CRF. The profile of previous OAB pharmacotherapy use will be evaluated in several ways as described below.

The number and percent of participants who had taken each type of previous OAB pharmacotherapy medication will be presented by WHO DDE base preferred name for each treatment group and overall.

The number of previous OAB medications taken per participant will be summarized by treatment group and overall. The duration of OAB pharmacotherapy and the reasons for its discontinuation (inadequate response, side effects or other) will also be summarized by treatment group and overall.

If a participant received multiple OAB medications before the study, the duration of treatment will be the sum of each duration of treatment if the time-period the participants was on these medications do not overlap each other. If a participant was taking multiple OAB medications at the same time, the duration of treatment will be “latest stop date of the overlapping medications – earliest start date of the overlapping medications”. Data will be summarized by treatment group and overall.

9.0 TREATMENT DURATION

Treatment duration for the Safety Population will be calculated as the number of days from the date of the first dose of study treatment to the date of exit, inclusive. Descriptive statistics (number of participants, mean, SD, median, first quartile, minimum, third quartile and maximum) will be presented by treatment group and overall.

In addition, treatment duration will also be summarized by presenting the number and percentage of participants whose time enrolled in the study satisfies the following time intervals: ≥ 1 day, ≥ 14 days, and ≥ 42 days, and 84 days.

The patient-years (total study duration across all participants in days/365.25), will also be presented for each treatment group and overall.

10.0 EXPLORATORY EFFICACY ANALYSES

As previously discussed, the main objective of Stage 1 of this study is to assess the safety of various doses of BOTOX intravesical instillation compared to placebo. However, exploratory analysis of select efficacy endpoints will also be performed.

The exploratory efficacy analyses will be based on the ITT Population. There will be no imputation of missing data. All analyses will be based on observed data only. Baseline for efficacy is defined as the last non-missing efficacy assessment before the first dose of study treatment.

10.1 EFFICACY VARIABLES

- Average number of UIE per day at baseline and each post-baseline visit.

  The number of UIEs per day will be recorded in the participant bladder diary over 3 consecutive days during the week prior to their baseline and each post baseline visit. The average number of UIE per day will be calculated as the total number of episodes recorded in the 3-day bladder diary divided by the total number of valid diary days (see section 15.2). Calculation of averages will employ only available data without imputation (for example, if bladder diary data is available for only 2 days of the consecutive 3-day period, then the denominator will be 2).

- Average number of Micturition Episodes per day at baseline and each post-baseline visit

  The number of micturition episodes per day will be calculated based on a consecutive 3-day average. This will be derived in a manner analogous to the average number of UIE per day.

- Average volume voided per day at baseline and each post-baseline visit

  The volume voided per micturition will be calculated from the total urine volume from micturitions (toilet voids or catheterizations) over one 24-hour period during the 3-day participant bladder diary divided by the number of micturitions in the same 24 hour period.

- Average number of urinary urgency episodes (UUE) per day at baseline and each post-baseline visit.

  This will be derived in a manner analogous to the average number of UIEs per day.

10.2 ANALYSIS METHODS

10.2.1 Change from Baseline Analyses

Baseline, raw values and change from baseline to week 12 will be performed using descriptive statistics by visit and treatment group for the following variables:

- Average number of UIEs per day
- Average number of micturition episodes per days
- Average volume voided per micturition
- Average number of UUE per day

10.2.2 Efficacy Listings

Each participants' bladder diary will be presented in a listing. Additionally, participant level listings will be provided displaying the raw and change from baseline values at each visit for the following urinary endpoints:

- average number of UIEs per day
- average number of UUEs per day
- average number of UUIEs per day
- average number of micturition episodes per day
- average number of nocturia episodes per day
- average volume voided per micturition

11.0 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. The safety measurements will include adverse events (AEs), clinical laboratory assessments, vital signs, physical examinations, post-void residual (PVR) urine volume, catheterization usage (in particular clean intermittent catheterization for urinary retention), and bladder and kidney ultrasound results. For each safety measurement, the last non-missing safety assessment before the first dose of study treatment will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of participants and mean, SD, median, first quartile, minimum, third quartile and maximum values. Categorical variables will be summarized by number and percentage of participants.

11.1 ADVERSE EVENTS

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

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 participants reporting TEAEs in each treatment group will be tabulated by descending percentage in any treatment group, by system organ class and preferred term, and further categorized by severity and causal relationship to the study drug and instillation procedure. If for a given preferred term more than 1 AE is coded to the same participant, the participant will be counted only once for that preferred term using the greatest severity for the summarization by severity and causal relationship.

Separate participant listings will be generated for deaths, serious adverse events, and TEAEs leading to study discontinuation.

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 listed by participant. The 39 terms are listed below.

MedDRA Preferred Terms Evaluated for Possible Distant Spread of Toxin

Cardiac Disorders
- Bradycardia

Eye Disorders
- Accommodation disorder
- Diplopia
- Extraocular 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

11.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented by treatment group for the following laboratory parameters:

Hematology: red blood cells (RBC); white blood cells (WBC); WBC differential (% and absolute): neutrophils, lymphocytes, monocytes, eosinophils, basophils, hematocrit, hemoglobin, platelets

Blood Chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT [SGPT]), aspartate aminotransferase (AST [SGOT]), total and direct bilirubin, blood urea nitrogen (BUN), calcium, chloride, creatinine, gamma glutamyltransferase (GGT), globulin, nonfasting glucose, potassium, total protein, and sodium

Urinalysis: color, appearance, specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin, urobilinogen, crystals; microscopic examination if positive for protein, leukocyte, occult blood, nitrite, or crystals

Urine dipstick: The urine dipstick reagent test is used to identify a potential UTI and to provide immediate information to the investigator. If positive for nitrites and/or leukocyte esterase, indicating a possible infection, the participant should be treated with antibiotics per the clinical judgment of the investigator and in accordance with local site practice.

Urine cytology: Urine cytology is performed at the screening visit only. Abnormal urine cytology suspicious for a urothelial malignancy should be investigated by the investigator according to local site practice, and only if such malignancy is ruled out should the participant be enrolled.

Urine pregnancy: Urine pregnancy testing will be conducted for women of childbearing potential.

PSA: Prostate-specific Antigen (PSA) levels will be measured at screening in male participants.

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 11.2–1. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values.

In addition, separate listings will be provided for each of the following clinical laboratory assessments:

- Participants with positive urine dipstick reagent test
- Participants with positive urine pregnancy test

Table 11.2–1. Criteria for Potentially Clinically Significant Laboratory Results

Parameter	*SI Unit*	*Lower Limit*	*Higher Limit*
CHEMISTRY			
Albumin	g/L	< 0.9 × LLN	> 1.1 × ULN
Alanine aminotransferase	U/L	—	≥ 3 × ULN
Alkaline phosphatase (AP)	U/L	—	≥ 3 × ULN
Aspartate aminotransferase	U/L	—	≥ 3 × ULN
Bilirubin, total	µmol/L	—	> 1.5 × ULN
Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Creatinine	µmol/L	—	> 1.3 × ULN
Glucose, nonfasting	mmol/L	< 0.8 × LLN	> 1.4 × ULN
Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Blood Urea Nitrogen (BUN)	mmol/L	—	> 1.2 × ULN
HEMATOLOGY			
Basophils, absolute cell count	10^9/L	—	> 3 × ULN
Eosinophils	10^9/L	—	> 1.5 × ULN
Hematocrit	Ratio	< 0.9 × LLN	> 1.1 × ULN
Hemoglobin	g/L	< 0.9 × LLN	> 1.1 × ULN
Lymphocytes	10^9/L	< 0.8 × LLN	> 1.2 × ULN
Monocytes	10^9/L	< 0.5 × LLN	> 2 × ULN
Neutrophils, absolute cell count	10^9/L	< 0.8 × LLN	> 1.5 × ULN
Platelet count	10^9/L	≤ 0.5 × LLN	≥ 1.5 × ULN
Red blood cell count	10^{12}/L	< 0.9 × LLN	> 1.1 × ULN
White blood cell count	10^9/L	≤ 0.7 × LLN	≥ 1.5 × ULN
URINALYSIS			
Glucose	mmol/L	—	Positive
pH	pH	< 0.9 × LLN	> 1.1 × ULN
Protein	g/L	—	Positive
Specific gravity	—	—	> 1.1 × ULN

LLN = lower limit of normal value provided by the laboratory; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal value provided by the laboratory.

11.3 VITAL SIGNS

Descriptive statistics for vital signs (systolic and diastolic blood pressure, pulse rate, temperature and body weight) and changes from baseline values at each visit and at the end of study will be presented by treatment group.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 11.3–1. The number and percentage of participants with PCS postbaseline values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values.

Table 11.3–1. Criteria for Potentially Clinically Significant Vital Signs

Parameter	***Flag***	***Criteria***[a]	
		Observed Value	*Change From Baseline*
Sitting systolic blood pressure, mm Hg	High	≥ 150	Increase of ≥ 20
	Low	< 90	Decrease of ≥ 20
Sitting diastolic blood pressure, mm Hg	High	≥ 100	Increase of ≥ 15
	Low	< 50	Decrease of ≥ 15
Sitting pulse rate, bpm	High	≥ 100	Increase of ≥ 15
	Low	< 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%

a A postbaseline value is considered potentially clinically significant if it meets both the observed-value and the change-from-baseline criteria.
bpm = beats per minute.

11.4 OTHER SAFETY PARAMETERS

11.4.1 Physical Examination

Physical examination will be performed at screening and at study exit visit. All findings at the screening visit will be recorded on the Medical and Surgical History/Physical Findings eCRF page. Any new or worsening condition observed at the study exit visit will be recorded on the Adverse Event eCRF page. Hence summaries for physical examinations will be captured in summaries presented for medical and surgical history and adverse events.

11.4.2 Post-Void Residual Urine Volume

Descriptive statistics for PVR urine volume (mL) and changes from baseline values at each visit and at the end of study will be presented by treatment group. In addition, the number and percentage of participants with PVR urine volume within each of the following categories will be presented by treatment group for each postbaseline visit as well as for the entire study:

- < 100 mL
- ≥ 100 mL and < 200 mL
- ≥ 200 mL and < 350 mL
- ≥ 350 mL

11.4.3 Bladder and Kidney Ultrasound

A listing of all participants with at least one pre-existing or new bladder or kidney condition will be provided for the Safety Population by treatment group.

11.4.4 Concurrent Procedures

Concurrent procedures will be presented in a listing together with the indication for which the procedure was performed. The indication will be coded using MedDRA system organ class and preferred term.

11.4.5 Catheterization Use

The number and proportion of participants catheterizing will be summarized, broken out by reason (for urinary retention or for other reasons) and whether it was CIC or not. This will be determined from the Catheterization eCRF. For the participants who initiate CIC for urinary retention post-instillation, the average number of catheterization urinary episodes per day will be calculated based on the bladder diary. These will be summarized by treatment group with descriptive statistics. The total duration of CIC usage for participants who do so for urinary retention post-instillation will be determined from the Catheterization eCRF and summarized using descriptive statistics by treatment group.

12.0 INTERIM ANALYSIS

No formal interim analysis is planned for this study. However, an independent data review committee (DRC) will review unblinded safety data from Stage 1 upon completion of the Week 6 post-instillation follow-up time point from each cohort. Based on the observed safety data from these reviews, the DRC will recommend to proceed with dose escalation from one cohort to the next. In addition, after review of the safety data in the 100 U and 300 U Cohorts, the DRC will recommend to proceed with dose escalation either to BOTOX 400 U followed by BOTOX 500 U or whether it is safe to proceed directly to BOTOX 500 U.

The DRC will also recommend to proceed with Stage 2 of the study and recommended the doses of BOTOX intravesical instillation for further investigation during Stage 2 based on an unblinded review of the safety data after completion of the Week 6 post-instillation follow-up time point of the 500 U Cohort in Stage 1 (stage 2 BOTOX doses will be 100 U, 300 U, 400 U and either a 500 U or a 200 U dose group).

If further safety data is required by the DRC prior to proceeding with dose escalation from one cohort (or stage) to the next, additional participants may be enrolled into a cohort as recommended by the DRC.

13.0 DETERMINATION OF SAMPLE SIZE

For Stage 1, approximately 50 to70 participants will be enrolled to ensure that 10 to 20 individuals are randomized into each of the 4 cohorts (100 U Cohort: n = 10; 300 U Cohort: n = 20; 400 U Cohort: n = 20; 500 U Cohort: n = 20) to provide sufficient data in the analysis and interpretation of safety results. Two adverse events of particular interest are urinary retention and urinary tract infection (UTI). From previous BOTOX studies, the percentage of participants in the BOTOX-treated population experiencing these adverse events is approximately 6% to 7% for urinary retention and 20% to 30% for UTI. In Cohort 1, the probability of observing at least one BOTOX-treated participant experiencing these adverse events is 0.39 to 0.44 and 0.83 to 0.94, respectively. For the other cohorts, the probability of observing at least one BOTOX-treated participant experiencing these adverse events is 0.63 to 0.69 and 0.97 to ~ 1, respectively.

14.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.3 (or newer) of SAS on a Linux operating system.

15.0 DATA HANDLING CONVENTIONS

15.1 STATISTICAL ANALYSIS VISIT WINDOWS

Table 15.1-1 presents the target visit day assigned for efficacy and safety analyses and the corresponding range of treatment days (statistical analysis window) during which an actual visit may occur.

Table 15.1–1. Statistical Analysis Visit Windows

Visit Timepoint	*Target Visit Day*[a]	*Statistical Analysis Window*
Screening/Baseline	NA	Days < Time of Study Treatment on Day 1
Day 1	Day 1	Day 1 from Time of Study Treatment to Midnight
Week 2	Day 15	Days [2, 29]
Week 6	Day 43	Days [30, 64]
Week 12	Day 85	≥ Day 65
End of Study[b]	Week 12 or Study Exit Visit	

a Relative to the date of the first dose of study treatment. Day 1 = the date of study treatment. There is no Day 0 or Week 0.

b Presented in analysis tables for safety parameters, including but not limited to clinical laboratory values, and vital signs. If a participant completes the study, the Week 12 visit is the end of study visit. If a participant discontinues the study prematurely, their last study visit (study exit visit) is the end of study visit.

If the assessment date (if the assessment date is unavailable, use visit date instead) is on or after the date of the first dose of study treatment, the study day is calculated by assessment date – date of the first dose of study treatment + 1. If the assessment date is before the date of the first dose of study treatment, the study day is calculated by assessment date – date of the first dose of study treatment. Therefore, a negative day indicates a day before the start of the study treatment. There is no Day 0; day of randomization and study treatment is Day 1.

If a participant has 2 or more visits within the same statistical analysis window, the last visit with a non-missing value will be used for analysis purposes for that corresponding visit timepoint. All postbaseline assessments will be considered for PCS categorization. All assessments will be included in respective listings.

15.2 DIARY DATA CONVENVENTIONS

[redacted]

[redacted]

15.3 DERIVED VARIABLES

The following criterion will be used to determine the category of urinary episode for each entry in a participant's bladder diary.

1. A participant has a **micturition episode** if the participant response is yes to either one of the following question in the bladder diary:
    - Did you urinate into the toilet or collection container?
    - Did you use a catheter to urinate?
2. A participant has a **urinary incontinence episode** if the participant response is yes to the following question in the bladder diary:
    - Did you have accidental urinary leakage?
3. A participant has an **urgency urinary incontinence episode** if the participant response is yes to both of the following two questions for one episode in the bladder diary:
    - Did you have accidental urinary leakage?
    - Was this episode associated with a sudden and urgent need to urinate?
4. A participant has an **urgency urinary episode** if the participant response is yes to the following question in the bladder diary:
    - Was this episode associated with a sudden and urgent need to urinate?

5. A participant has a **nocturia episode** if the participant response is yes to the following question in the bladder diary:
    - Did this episode wake you from night sleep?

6. A participant has a **catheterization episode** if the participant response is yes to the following question in the bladder diary:
    - Did you use a catheter to urinate?

The average volume voided per micturition will be calculated using the bladder diary records within the 24-hour period where participants were required to collect and record the urine volume from each urinary episode. To obtain this value, the total volume voided will be calculated as the sum of the volume voided from the bladder diary records where urine volume was collected within this 24-hour period. The total volume voided will then be divided by the number of bladder diary records that were included in the sum.

15.4 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a participant has repeated assessments before the start of the first treatment, the results from the last non-missing assessment made prior to the start of the study treatment will be used as baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last non-missing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

15.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study treatment, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

15.6 MISSING CAUSAL RELATIONSHIP TO STUDY TREATMENT FOR ADVERSE EVENTS

If the causal relationship to the study treatment is missing for an AE that started on or after the date of the first dose of study treatment, a causality of yes will be assigned. The imputed values for causal relationship to study treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

15.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study treatment, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of study treatment, the date of the first dose of study treatment will be assigned to the missing start date

- If the stop date is before the date of the first dose of study treatment, the stop date will be assigned to the missing start date

15.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

15.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study treatment, the first day of the month will be assigned to the missing day

15.8.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study treatment is missing, impute it as the date of the End of Study Visit (see section 15.1). If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of study treatment, the month and day of the last dose of study treatment will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the last dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the last dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of study treatment, the day of the last dose of study treatment will be assigned to the missing day

- If either the year of the incomplete stop date is before the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete stop date is after the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of study treatment, the first day of the month will be assigned to the missing day

15.9 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

Table 15.9–1 shows examples of how some possible laboratory results should be coded for the analysis.

Table 15.9–1. Examples of Coding Special Character Values for Clinical Laboratory Parameters

Laboratory Test, SI Unit	***Possible Laboratory Results***	***Coded Value for Analysis***
CHEMISTRY		
ALT, U/L	< 5	5
AST, U/L	< 5	5
Bilirubin, total, µmol/L	< 2	2
URINALYSIS		
Glucose, mmol/L	= OR > 55, ≥ 55, > 0	Positive
	≤ 0, negative	Negative
pH	> 8.0, ≥ 8.0	8.0
	≥ 8.5	8.5
Protein	= OR > 3.0, ≥ 3.0, > 0	Positive
	≤ 0	Negative

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SI = *Le Système International d'Unités* (International System of Units).

16. Amendments

Date	Revision Number	Primary Author	Description of Change
08 Jan 2018	1	Andrew Magyar	Initial Approval
07 Mar 2019	2	Emily Weng	• Clarified the definition of Concomitant medication to also include encompass all medicinal products that the participant was taking prior to the first dose of study treatment and which are going at this visit in. Section 8.4 • Added the analyses in Section 10.1 and 10.2: average number of micturition episodes per day and average volume voided per day • Replaced the regression analyses with descriptive statistics in Section 10.2 • Removed responder analyses in Section 10.3 and

			time to event analyses in Sections 10.4 and 15.3 • Clarifications for Section 6.1 per the new updated in Sections 10.1, 10.2 and 10.3. • Changed the analysis of study duration to treatment duration. • Administrative changes

ALLERGAN

1839-201-021 Statistical Analysis Plan for Stage 1-Final

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
07-Mar-2019 14:01 GMT-080	[redacted]	Clinical Development Approval
07-Mar-2019 15:16 GMT-080		Biostatistics Approval
07-Mar-2019 16:45 GMT-080		Clinical Development Approval
08-Mar-2019 08:31 GMT-080		Biostatistics Approval
08-Mar-2019 12:15 GMT-080		Biostatistics Approval

1.0 TITLE PAGE

1839-201-021

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Single-treatment, 2-stage, Dose-finding Study Evaluating the Efficacy and Safety of BOTOX® Intravesical Instillation in Participants with Overactive Bladder and Urinary Incontinence

STATISTICAL ANALYSIS PLAN for Stage 2- Clinical Study Report

Final: 10 Jan 2020

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
BOTOX	Botulinum Toxin Type A Purified Neurotoxin Complex (US Adopted Name is onabotulinumtoxinA)
CIC	clean intermittent catheterization
DRC	data review committee
eCRF	electronic case report form
FSV	first sensation to void
HRQL	health-related quality of life
Hydrogel	Hydrogel refers to RTGel™ [redacted]
IDC	involuntary detrusor contraction
ITT	intent to treat
LOCF	last observation carried forward
MCC	maximum cystometric capacity
OAB	overactive bladder
[redacted]	
PCS	potentially clinically significant
[redacted]	
PID	participant identification
[redacted]	
PSA	prostate-specific antigen
PVR	Post-void residual
Pdetmax	maximum detrusor pressure
SAE	Serious adverse event
SAP	statistical analysis plan

SD	standard deviation
SE	standard error
UIE	urinary incontinence episode
UTI	urinary tract infection
UUE	urinary urgency episode
UUIE	urinary urgency incontinence episode
SI	*Le Système International d'Unités* (International System of Units)
TEAE	treatment-emergent adverse event

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data specified in the final protocol of Study 1839-201-021 (version dated 8 June 2017) and the most recent amendment (amendment 2 dated 20 Dec 2018). Specifications of tables, figures, and data listings are contained in a separate document. There are two stages in this study. This SAP is for Stage 2 of the study. The SAP for Stage 1 of the study will be prepared in a separate document. Stage 1 and Stage 2 data will be analyzed separately. In addition, adverse event data for the first 12 weeks (84 days) from each stage of the study will be pooled.

This study is a phase 2, multicenter, randomized, double-blind, placebo-controlled, single-treatment, 2-stage, dose-finding study for participants with overactive bladder (OAB) and urinary incontinence who are inadequately managed by pharmacologic therapies. The 2-stage study design allows for an assessment of safety during Stage 1 in a conservative, placebo-controlled dose-escalating manner prior to the initiation of Stage 2 where the efficacy and safety of BOTOX instillation will be evaluated in a placebo-controlled, parallel group, dose-finding design.

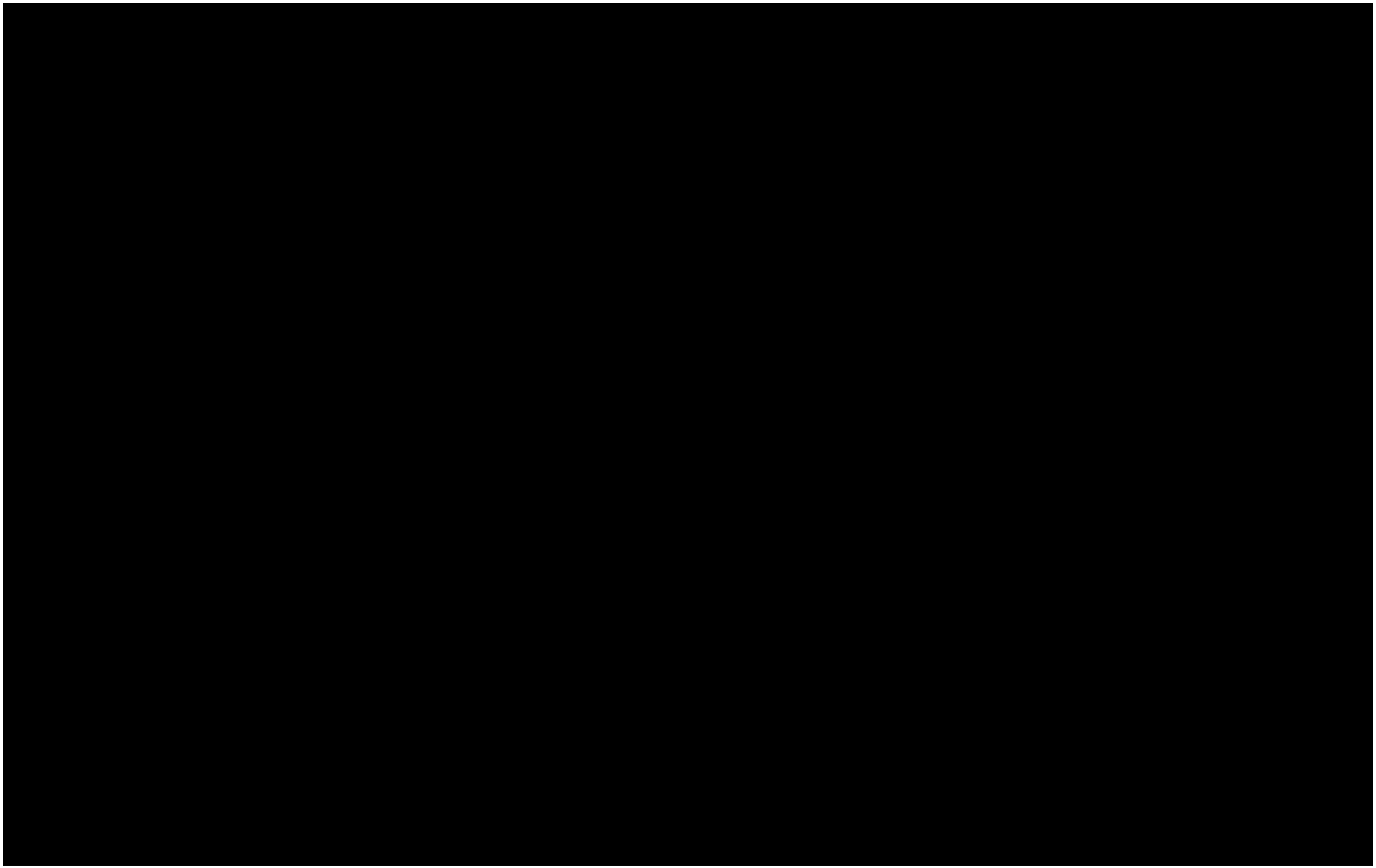
Total duration of participation in Stage 2 is 28 weeks, including a 4-week screening and 24-week treatment/follow-up period. The schedule of activities is presented in Table 4-1.

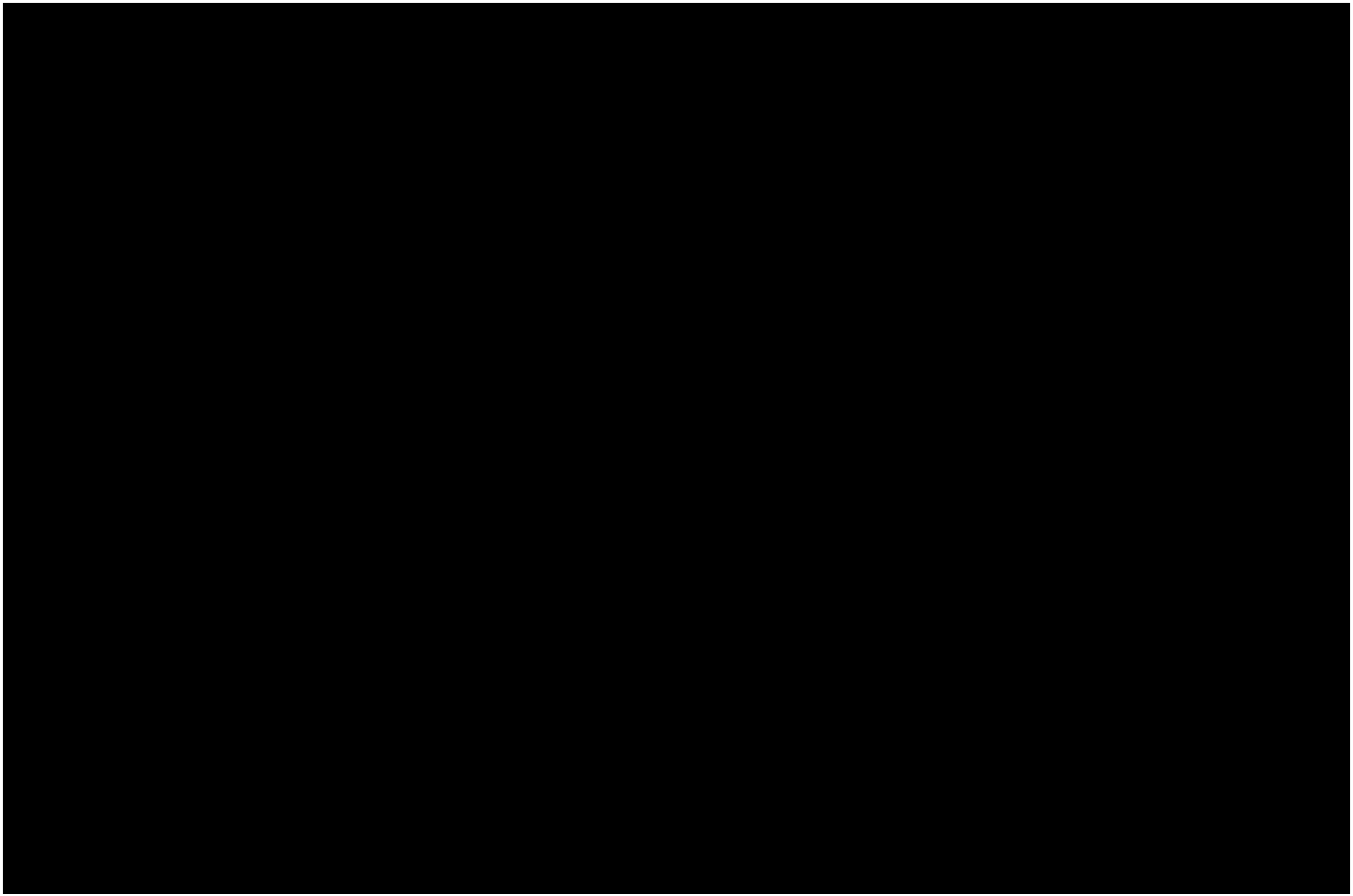
Stage 2 will investigate 4 doses of BOTOX (100 U, 300 U, 400 U, 500 U [or 200 U]) compared to placebo in a 1:1:1:1:1 ratio. A total of 265 randomized participants are required for Stage 2. Depending on the outcome of Data review committee (DRC) review of safety results from the 500 U Cohort in Stage 1, BOTOX 500 U may be replaced with a BOTOX 200 U treatment group (Figure 4-1).

BOTOX or placebo in a Hydrogel admixture will be instilled into the bladder as a single intravesical instillation through a sterile, single use catheter using aseptic technique per local site practice. The total volume to be instilled will be 60 mL.

Figure 4-1 Study Design Diagram

Stage 2 will begin after confirmation of the 4 BOTOX doses for investigation in Stage 2 based on unblinded review of safety results from the 500 U Cohort in Stage 1 by the DRC





5.0 OBJECTIVES

- To compare the efficacy of a single treatment of BOTOX intravesical instillation, with possible doses ranging from 100 U up to 500 U, with placebo in participants with OAB and urinary incontinence.

- To compare the safety of a single treatment of BOTOX intravesical instillation, with possible doses ranging from 100 U to up to 500 U, with placebo in participants with OAB and urinary incontinence

6.0 PARTICIPANT POPULATIONS

6.1 INTENT-TO-TREAT POPULATION

The Intent-to-Treat (ITT) Population will consist of all randomized participants. All efficacy data will be analyzed as randomized using the ITT Population. The primary efficacy analysis will be performed in Stage 2 on the ITT population when all study participants reach Week 12.

6.2 SAFETY POPULATION

The Safety Population will consist of all participants enrolled in the study who received the study treatment.

7.0 PARTICIPANT DISPOSITION

The number and percentage of participants in the study populations (Safety and ITT) will be summarized by treatment group; the overall number of participants screened will also be presented.

The number and percentage of participants who complete the study and of participants who prematurely discontinue the study will be presented for each treatment group and pooled across treatment groups for the ITT population. The reasons for premature discontinuation from the study as recorded on the termination pages of the electronic case report forms will be summarized (number and percentage) by treatment group for the ITT population. All participants who prematurely discontinue during the study will be listed by discontinuation reason for the ITT population.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

All continuous variables will be summarized by number of participants and mean, SD, first quartile, median, minimum, third quartile, and maximum values. Categorical variables will be summarized by number and percentage of participants. All summaries will be performed on the ITT population.

Demographic parameters (age; age group; race; ethnicity; sex), baseline characteristics (weight; height; and body mass index, calculated as weight [kg]/(height [m])^2) will be summarized descriptively by treatment group.

The following baseline disease characteristics will be summarized descriptively by treatment group and overall (i.e. pooled across all treatment groups): duration of OAB (in years), average number of UIE, UUIE, UUE, micturition episodes & nocturia episodes per day, volume voided per micturition and PVR urine volume.

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants with medical history ongoing at screening will be summarized by system organ class, preferred term and treatment group. Data for medical history that is not ongoing at screening will be summarized and presented in a similar manner. An overall total will be provided for the study as well as by treatment group.

Prior medication is defined as any medication taken before the date of the first dose of study treatment. Concomitant medication is defined as any medication taken on or after the date of the first dose of study treatment.

Both prior and concomitant medications will be coded using the Anatomical-Therapeutic-Chemical classification text from World Health Organization (WHO) Drug Dictionary. The use of prior and concomitant medications will be summarized by the number and percentage of participants in each treatment group and overall.

Previous pharmacotherapy for OAB are medications that were taken before the first study drug (BOTOX or placebo + Hydrogel admixture) instillation. Information on these is captured in the correspondingly named CRF. The profile of previous OAB pharmacotherapy use will be evaluated in several ways as described below:

- The number and percent of participants who had taken each type of previous OAB pharmacotherapy medication will be presented by WHO DDE base preferred name for each treatment group and overall.

- The number of previous OAB medications taken per participant will be summarized by treatment group and overall. The duration of OAB pharmacotherapy and the reasons for its discontinuation (inadequate response, side effects or other) will also be summarized by treatment group and overall.

- If a participant received multiple OAB medications before the study, the duration of treatment will be the sum of each duration of treatment if the time-period the participants was on these medications do not overlap each other. If a participant was taking multiple OAB medications at the same time, the duration of treatment will be "latest stop date of the overlapping medications – earliest start date of the overlapping medications." Data will be summarized by treatment group and overall.

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 EXTENT OF EXPOSURE

Number of participants who have received single intravesical instillation during study will be summarized by treatment group.

Study duration for the Safety Population will be calculated as the number of days from the date of the first dose of study treatment to the date of the study exit, inclusive. Descriptive statistics (number of participants, mean, SD, median, first quartile, minimum, third quartile and maximum) will be presented by treatment group and overall.

In addition, study duration will also be summarized by presenting the number and percentage of participants whose time enrolled in the study satisfies the following time intervals: ≥ 1 day, ≥ 2 weeks (14 days), ≥ 6 weeks (42 days), ≥ 12 weeks (84 days), ≥ 16 weeks (112 days), ≥ 20 weeks (140 days), and ≥ 24 weeks (168 days).

9.2 MEASUREMENT OF TREATMENT COMPLIANCE

Not applicable in this study.

10.0 EFFICACY ANALYSES

The efficacy analyses will be based on the ITT Population. *Baseline* for efficacy is defined as the last nonmissing assessment before the first dose of study treatment. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise. There will be no adjustments for multiple comparisons.

Mis-stratified participants, if any, will be analyzed based on the stratification group to which the participants were assigned to (i.e. the planned stratification group used at the time of randomization).

Unless otherwise stated, missing values will be imputed (see details below) only for the primary efficacy variable.

10.1 PRIMARY EFFICACY VARIABLE

The primary efficacy variable is the change from baseline in the average number of urinary incontinence episodes (UIEs) per day. The primary timepoint is week 12.

The number of UIEs per day will be recorded in the participant bladder diary over 3 consecutive days at any time during the screening period for the screening diary, and over 3 consecutive days during the week prior to each post baseline visit. The average number of UIEs per day will be calculated as the total number of episodes recorded in the 3-day bladder diary divided by the total number of valid diary days (see Section 15.2). Calculation of averages will employ available "valid diary days" data without imputation. If no "valid diary days" data are available for the consecutive 3-day period, that average will be considered missing for that participant. The last-observation-carried-forward (LOCF) approach will be used to impute missing postbaseline average values.

For the primary efficacy analysis, the null hypothesis is that there is no difference between each (BOTOX and Hydrogel admixture group) and (placebo and Hydrogel admixture) in the mean change from baseline in daily average number of UIEs at week 12. The alternative hypothesis is that there is a difference between each (BOTOX and Hydrogel admixture group) and (placebo and Hydrogel admixture group) in the mean change from baseline in daily average number of UIEs at week 12.

The hypotheses will be tested using an ANCOVA model with baseline value as covariate and treatment group and sex (male, female) as factors. Pairwise comparisons will be performed for each BOTOX group versus placebo using t-tests of the least square means from the ANCOVA model. The stratification factor of baseline UUIEs (≤ 9 or > 9 episodes/day) is not included in the model due to a very high correlation between UIEs and UUIEs (Pearson's correlation coefficient = 0.97 based on phase 2 data (191622-077 study)).

A sensitivity analysis of the primary efficacy variable will be performed using the same ANCOVA model discussed above. This will be based on observed data only (i.e. no LOCF imputation of missing postbaseline average values).

10.2 SECONDARY EFFICACY VARIABLES

The secondary efficacy variables are:

- change from baseline to week 12 in the average number of micturition episodes per day (toilet voids or catheterizations)
- change from baseline to week 12 in the average volume voided per micturition

The number of micturition episodes per day will be calculated based on a consecutive 3-day average. This will be derived in a manner analogous to the average number of UIEs per day.

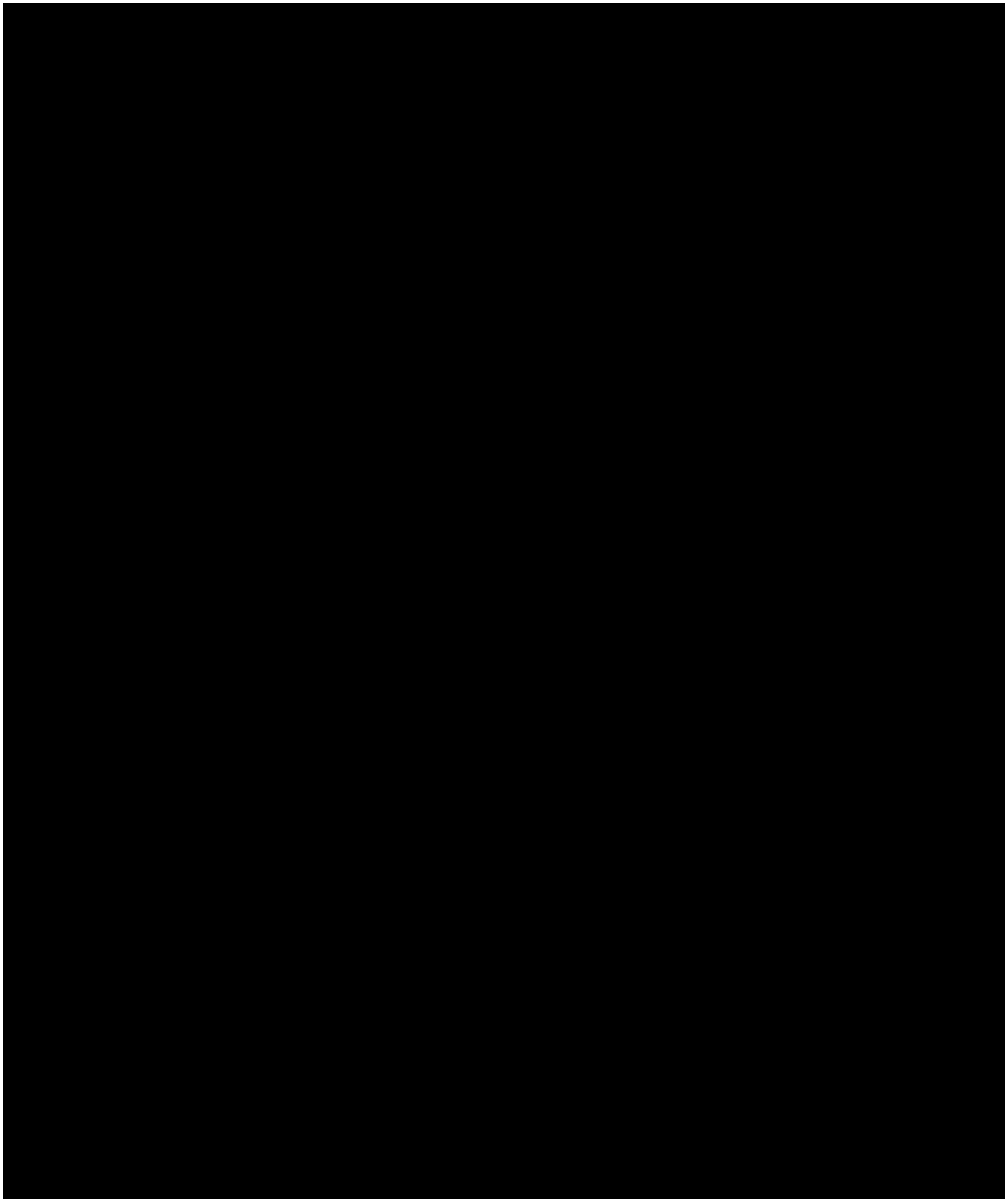
The average volume voided per micturition will be calculated using the bladder diary records within the 24-hour period where participants were required to collect and record the urine volume from each urinary episode. To obtain this value, the total volume voided (from toilet voids or catheterizations) will be calculated as the sum of the volume voided from the bladder diary records where urine volume was collected within this 24-hour period. The total volume voided will then be divided by the number of micturitions in the same 24-hour period that were included in the sum.

Only data from "valid diary days" will be used in the calculations of the averages discussed above.

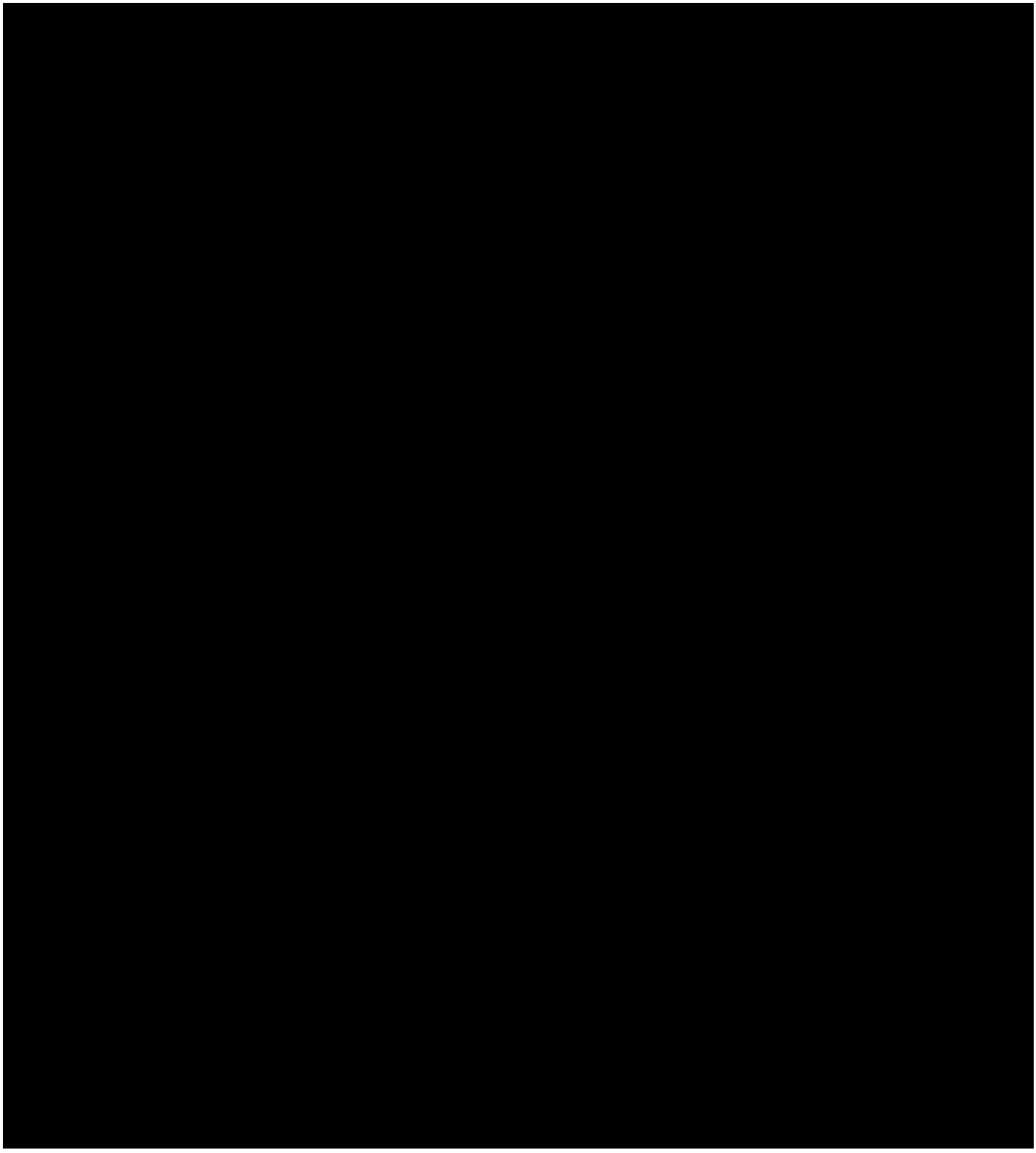
The change from baseline in the average number of micturition episodes per day will be analyzed using an ANCOVA model with baseline as covariate and treatment group and sex (male, female) as factors.

The change from baseline in the average volume voided per micturition will be analyzed using an ANCOVA model with baseline as covariate and treatment group, sex (male, female) and baseline UUIEs (≤ 9 or > 9 episodes/day) as factors.

[redacted]



[redacted]



11.0 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs) and clinical laboratory, vital sign physical examinations, post-void residual (PVR) urine volume, catheterization usage (in particular clean intermittent catheterization (CIC) for urinary retention), and bladder and kidney ultrasound results. For each safety measurement the last nonmissing safety assessment before the first dose of study treatment will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of participants and mean, SD, median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

11.1 ADVERSE EVENTS

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

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 participants reporting TEAEs in each treatment group will be tabulated by descending percentage in any treatment group, by system organ class and preferred term, and further categorized by severity and causal relationship to the study drug and instillation procedure. If for a given preferred term more than 1 AE is coded to the same participant, the participant will be counted only once for that preferred term using the greatest severity for the summarization by severity and causal relationship.

Separate participant listings will be generated for deaths, serious adverse events, and TEAEs leading to study discontinuation.

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 listed by participant. The 39 terms are listed below.

MedDRA Preferred Terms Evaluated for Possible Distant Spread of Toxin

Cardiac Disorders
- Bradycardia

Eye Disorders
- Accommodation disorder
- Diplopia
- Extraocular 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

11.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented by treatment group for the following laboratory parameters:

Hematology: red blood cells (RBC); white blood cells (WBC); WBC differential (% and absolute): neutrophils, lymphocytes, monocytes, eosinophils, basophils, hematocrit, hemoglobin, platelets

Blood Chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT [SGPT]), aspartate aminotransferase (AST [SGOT]), total and direct bilirubin, blood urea nitrogen (BUN), calcium, chloride, creatinine, gamma glutamyltransferase (GGT), globulin, nonfasting glucose, potassium, total protein, and sodium

Urinalysis: color, appearance, specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin, urobilinogen, crystals; microscopic examination if positive for protein, leukocyte, occult blood, nitrite, or crystals

Urine dipstick: The urine dipstick reagent test is used to identify a potential UTI and to provide immediate information to the investigator. If positive for nitrites and/or leukocyte esterase, indicating a possible infection, the participant should be treated with antibiotics per the clinical judgment of the investigator and in accordance with local site practice.

Urine cytology: Urine cytology is performed at the screening visit only. Abnormal urine cytology suspicious for a urothelial malignancy should be investigated by the investigator according to local site practice, and only if such malignancy is ruled out should the participant be enrolled.

Urine pregnancy: Urine pregnancy testing will be conducted for women of childbearing potential.

PSA: Prostate-specific Antigen (PSA) levels will be measured at screening in male participants.

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 11.2–1. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with available non-PCS baseline values and at least 1 postbaseline assessment for the double-blind treatment period. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value for the double-blind treatment period. A supportive tabular display of participants with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values.

In addition, separate listings will be provided for each of the following clinical laboratory assessments:

- Participants with positive urine dipstick reagent test
- Participants with positive urine pregnancy test

Shift tables from baseline to end of study for clinical laboratory parameters will be presented by treatment group for the following categories: low, normal, and high, which are provided by lab vendor.

Table 11.2–1 Criteria for Potentially Clinically Significant Laboratory Results

Parameter	*SI Unit*	*Lower Limit*	*Higher Limit*
CHEMISTRY			
Albumin	g/L	< 0.9 × LLN	> 1.1 × ULN
Alanine aminotransferase	U/L	—	≥ 3 × ULN
Alkaline phosphatase (AP)	U/L	—	≥ 3 × ULN
Aspartate aminotransferase	U/L	—	≥ 3 × ULN
Bilirubin, total	µmol/L	—	> 1.5 × ULN
Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Creatinine	µmol/L	—	> 1.3 × ULN
Glucose, nonfasting	mmol/L	< 0.8 × LLN	> 1.4 × ULN
Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Blood Urea Nitrogen (BUN)	mmol/L	—	> 1.2 × ULN
HEMATOLOGY			
Basophils, absolute cell count	10^9/L	—	> 3 × ULN
Eosinophils	10^9/L	—	> 1.5 × ULN
Hematocrit	Ratio	< 0.9 × LLN	> 1.1 × ULN
Hemoglobin	g/L	< 0.9 × LLN	> 1.1 × ULN
Lymphocytes	10^9/L	< 0.8 × LLN	> 1.2 × ULN
Monocytes	10^9/L	< 0.5 × LLN	> 2 × ULN
Neutrophils, absolute cell count	10^9/L	< 0.8 × LLN	> 1.5 × ULN
Platelet count	10^9/L	≤ 0.5 × LLN	≥ 1.5 × ULN
Red blood cell count	10^{12}/L	< 0.9 × LLN	> 1.1 × ULN
White blood cell count	10^9/L	≤ 0.7 × LLN	≥ 1.5 × ULN
URINALYSIS			
Glucose	mmol/L	—	Positive
pH	pH	< 0.9 × LLN	> 1.1 × ULN
Protein	g/L	—	Positive
Specific gravity	—	—	> 1.1 × ULN

LLN = lower limit of normal value provided by the laboratory; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal value provided by the laboratory.

11.3 VITAL SIGNS

Descriptive statistics for vital signs (systolic and diastolic blood pressures, pulse rate, temperature and weight) and changes from baseline values at each visit will be presented by treatment group.

Vital sign values will be considered PCS if they meet both the observed-value criteria and the change-from-baseline criteria listed in Table 11.3-1. The number and percentage of participants with PCS postbaseline values will be tabulated by treatment group. The percentages will be calculated relative to the number of participants with available baseline values and at least 1 postbaseline assessment. The numerator will be the total number of patients with available baseline values and at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values.

Table 11.3-1. Criteria for Potentially Clinically Significant Vital Signs

Parameter	***Flag***	***Criteria[a]***	
		Observed Value	*Change From Baseline*
Sitting systolic blood pressure, mm Hg	High	≥ 150	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Sitting diastolic blood pressure, mm Hg	High	≥ 100	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Sitting pulse rate, bpm	High	≥ 100	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%
Temperature, °C	High	> 38	—
	Low	< 35	—

a A postbaseline value is considered potentially clinically significant if it meets both the observed-value and the change-from-baseline criteria.
bpm = beats per minute.

11.4 OTHER SAFETY PARAMETERS

11.4.1 Physical Examination

Physical examination will be performed at screening and at study exit visit. All findings at the screening visit will be recorded on the Medical and Surgical History/Physical Findings eCRF page. Any new or worsening condition observed at the study exit visit will be recorded on the Adverse Event eCRF page. Hence summaries for physical examinations will be captured in summaries presented for medical and surgical history and adverse events.

11.4.2 Post-Void Residual Urine Volume

Descriptive statistics for PVR urine volume (mL) and changes from baseline values at each visit and at the end of study will be presented by treatment group. In addition, the number and percentage of participants with PVR urine volume within each of the following categories will be presented by treatment group for each postbaseline visit as well as for the entire study:

- < 100 mL
- ≥ 100 mL and < 200 mL
- ≥ 200 mL and < 350 mL
- ≥ 350 mL

11.4.3 Bladder and Kidney Ultrasound

A listing of all participants with at least one pre-existing or new bladder or kidney condition will be provided for the Safety Population by treatment group.

11.4.4 Concurrent Procedures

Concurrent procedures will be presented in a listing together with the indication for which the procedure was performed. The indication will be coded using MedDRA system organ class and preferred term.

11.4.5 Catheterization Use

The number and proportion of participants catheterizing will be summarized, broken out by reason (for urinary retention or for other reasons) and whether it was CIC or not. This will be determined from the Catheterization eCRF.

12.0 INTERIM ANALYSIS

No interim analysis is planned for this study. However, in Stage 2, a primary analysis will be conducted when all randomized participants have completed at least 12 weeks of follow-up post-randomization (or prematurely exited the study prior to Week 12). The final analysis will be performed after study completion. There will be 2 database locks for Stage 2: one for primary and one for final analysis.

The purpose of the primary analysis is to identify early trends in the data for administrative planning of phase 3 studies. Specifications of tables, figures, and data listings to be generated during the primary analysis are provided in a separate document.

On completion of the primary analysis, the study will be unblinded to Allergan personnel. However, investigators and study sites personnel will remain blinded until completion of the final analysis.

13.0 DETERMINATION OF SAMPLE SIZE

For Stage 2, 50 participants are required for each of the 4 BOTOX treatment groups and 50 participants are required for the placebo group in order to obtain approximately 72% power to detect a between group difference of 1.8 episodes in change from baseline to week 12 in the number of episodes of urinary incontinence per day between the BOTOX and placebo treatment groups. Sample size calculations are based on a two-sample t-test assuming a common standard deviation (SD) of 3.5 episodes and a 2-sided type I error rate of 0.05. In order to account for participant attrition (estimated to be 5%), the sample size was increased to 53 participants for each treatment group, amounting to a total of 265 randomized participants required for Stage 2. Additionally, using these samples sizes, the probability of observing at least one occurrence of urinary retention or UTI in the BOTOX-treated population in Stage 2 is nearly 1.

14.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.2 (or newer) of SAS on a Linux operating system.

15.0 DATA HANDLING CONVENTIONS

15.1 STATISTICAL ANALYSIS VISIT WINDOWS

Table 15.1-1 presents the visits assigned for efficacy and safety analyses and the corresponding range of treatment days (window) during which an actual visit may occur.

Table 15.1-1. Statistical Analysis Visit Windows

Derived Visit	*Scheduled Visit Day*[a]	*Window*
Baseline	Day 1	Days ≤ 1
Week 2	Day 15	Days [2, 29]
Week 6	Day 43	Days [30, 64]
Week 12	Day 85	Days [65, 99]
Week 16	Day 113	Days [100, 127]
Week 20	Day 141	Days [128, 155]
Week 24	Day 169	Days ≥ 156
End of study[b]	Week 24 or Study Exit Visit	

a Relative to the date of the study treatment. Day 1 = the date of the study treatment.

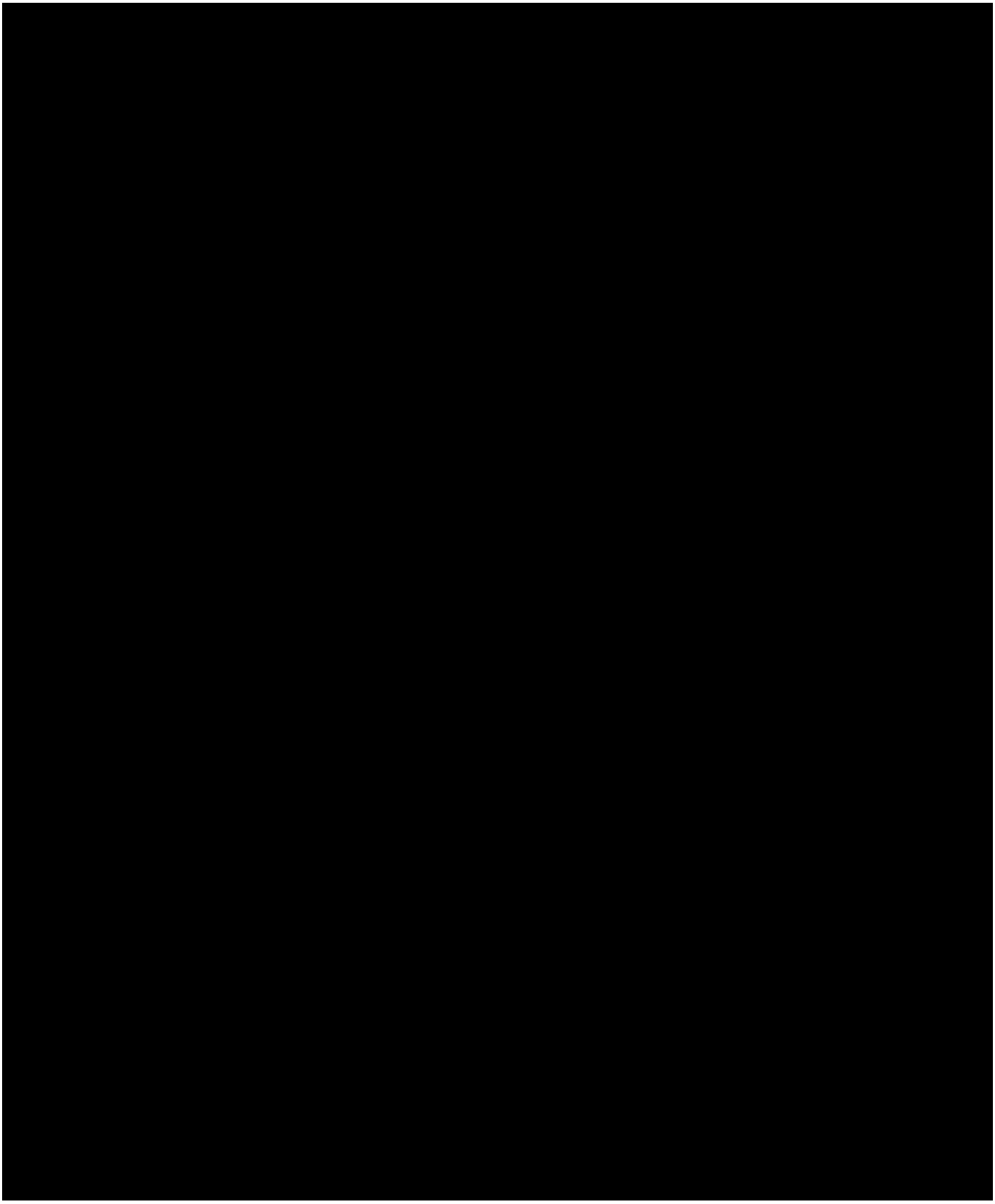
b Presented in analysis tables for safety parameters, including but not limited to electrocardiograms, clinical laboratory values, and vital signs. If a participant completes the study, the Week 24 visit is the end of study visit. If a participant discontinues the study prematurely, their last study visit (study exit visit) is the end of study visit.

If the assessment date (if the assessment date is unavailable, use visit date instead) is on or after the date of the of study treatment, the study day is calculated by assessment date – date of the of study treatment + 1. If the assessment date is before the date of the study treatment, the study day is calculated by assessment date – date of the study treatment. Therefore, a negative day indicates a day before the start of the study treatment. There is no Day 0; day of randomization and study treatment is Day 1.

If a participant has 2 or more visits within the same window, the last visit with a nonmissing value will be used for analysis. All postbaseline assessments will be considered for PCS categorization. All assessments will be included in respective listings.

15.2 DIARY DATA CONVENTIONS

[redacted]



[redacted]

15.3 DERIVED VARIABLES

The following criterion will be used to determine the category of urinary episode for each entry in a participant's bladder diary.

1. A participant has a **micturition episode** if the participant response is yes to either one of the following question in the bladder diary:
    - Did you urinate into the toilet or collection container?
    - Did you use a catheter to urinate?
2. A participant has a **urinary incontinence episode (UIE)** if the participant response is yes to the following question in the bladder diary:
    - Did you have accidental urinary leakage?
3. A participant has a **urinary urgency incontinence episode (UUIE)** if the participant response is yes to both of the following two questions for one episode in the bladder diary:
    - Did you have accidental urinary leakage?
    - Was this episode associated with a sudden and urgent need to urinate?
4. A participant has a **urinary urgency episode (UUE)** if the participant response is yes to the following question in the bladder diary:
    - Was this episode associated with a sudden and urgent need to urinate?
5. A participant has a **nocturia episode** if the participant response is yes to the following question in the bladder diary:
    - Did this episode wake you from night sleep?

6. A participant has a **catheterization episode** if the participant response is yes to the following question in the bladder diary:

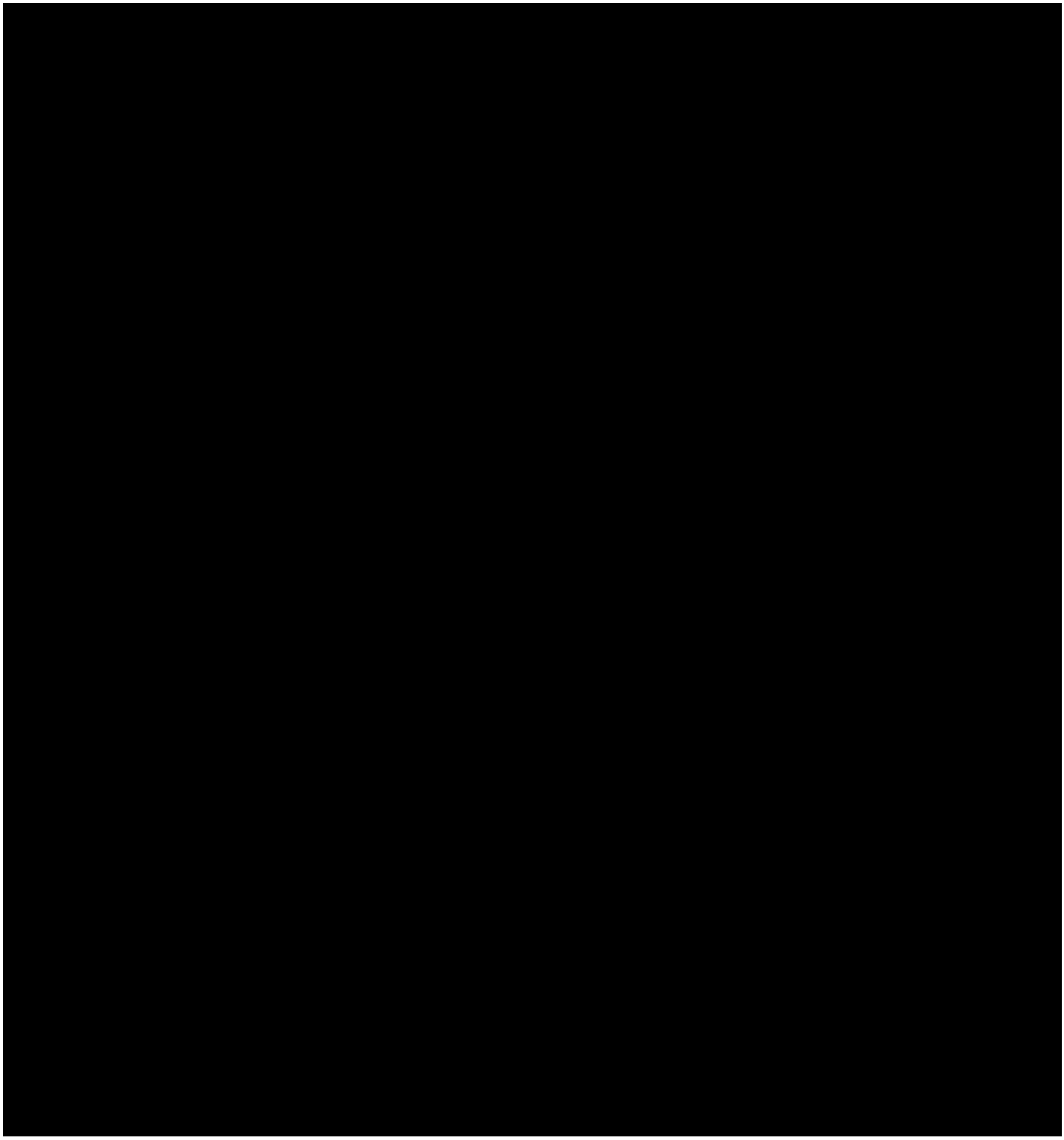
    - Did you use a catheter to urinate?

The number of UIEs per day will be recorded in the participant bladder diary over 3 consecutive days at any time during the screening period for the screening diary, and over 3 consecutive days during the week prior to each post baseline visit. The average number of UIEs per day will be calculated as the total number of episodes recorded in the 3-day bladder diary divided by the total number of valid diary days (see Section 15.2). The average number of micturition episodes, UUIEs, UUEs, and nocturia episodes will be derived in a similar manner.

To determine stratification groups (≤ 9 or > 9 UUIEs/day) for participants during randomization, the concept of valid diary days was not used by investigators to calculate the average number of UUIEs per day. Instead, all UUIEs recorded on the bladder diary from the beginning to the end of the first 3 consecutive 24 hour periods during the screening period was used irrespective of whether it was a valid dairy day or not. After database lock, this calculation will be repeated see if the values obtained by Allergan (i.e. actual stratification group) is the same as that recorded by investigators in the IVRS (planned stratification group). Note that this is done only to check for mis-stratifications. All other analyses or derivations using bladder diary data will be based on valid diary days.

The average volume voided per micturition will be calculated using the bladder diary records within the 24-hour period where participants were required to collect and record the urine volume from each urinary episode. To obtain this value, the total volume voided will be calculated as the sum of the volume voided from the bladder diary records where urine volume was collected within this 24-hour period. The total volume voided will then be divided by the number of bladder diary records that were included in the sum.

[redacted]



15.4 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a participant has repeated assessments before the start of the study treatment, the results from the final nonmissing assessment made prior to the start of the study treatment will be used as baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last nonmissing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

15.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the dose of study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the dose of study treatment, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

15.6 MISSING CAUSAL RELATIONSHIP TO STUDY DRUG FOR ADVERSE EVENTS

If the causal relationship to the study treatment is missing for an AE that started on or after the date of the dose of study treatment, a causality of yes will be assigned. The imputed values for causal relationship to study treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

15.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the dose of study treatment, the month and day of the dose of study treatment will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the dose of study treatment, *December 31* will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the dose of study treatment, the day of the dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the dose of study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the dose of study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the dose of study treatment, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the dose of study treatment, the date of the dose of study treatment will be assigned to the missing start date

- If the stop date is before the date of the dose of study treatment, the stop date will be assigned to the missing start date

15.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including rescue medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first.

15.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the dose of study treatment, the month and day of the dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the dose of study treatment, the day of the dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the dose of study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the dose of study treatment, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the dose of study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the dose of study treatment, the first day of the month will be assigned to the missing day

15.8.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the study exit is missing, impute it as last visit date recorded. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the study exit, the month and day of the last dose of study treatment will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the study exit, *December 31* will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the study exit, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the study exit, the day of the study exit will be assigned to the missing day

- If either the year of the incomplete stop date is before the year of the date of the study exit or if both years are the same but the month of the incomplete stop date is before the month of the date of the study exit, the last day of the month will be assigned to the missing day

- If either the year of the incomplete stop date is after the year of the date of the study exit or if both years are the same but the month of the incomplete stop date is after the month of the date of the study exit, the first day of the month will be assigned to the missing day

15.9 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table because, for example, a character string is reported for a parameter of the numeric type, a coded value must be appropriately determined for use in the statistical analyses. The actual values, however, as reported in the database will be presented in the data listings.

shows examples of how some possible laboratory results should be coded for the analysis Table 15.9-1.

Table 15.9-1 Examples of Coding Special Character Values for Clinical Laboratory Parameters

Laboratory Test, SI Unit	***Possible Laboratory Results***	***Coded Value for Analysis***
CHEMISTRY		
ALT, U/L	< 5	5
AST, U/L	< 5	5
Bilirubin, total, µmol/L	< 2	2
URINALYSIS		
Glucose, mmol/L	= OR > 55, ≥ 55, > 0	Positive
	≤ 0, negative	Negative
pH	> 8.0, ≥ 8.0	8.0
	≥ 8.5	8.5
Protein	= OR > 3.0, ≥ 3.0, > 0	Positive
	≤ 0	Negative

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SI = *Le Système International d'Unités* (International System of Units).

16.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

It is stated in protocol that all ANCOVA models will include both stratification factors (sex and baseline UUIEs per day) as independent variables. However, some of the ANCOVA models include only sex (male, female) due to the high correlation (observed in previous Allergan studies) between baseline UUIEs (≤ 9 or > 9 episodes/day) and some of the dependent variables derived from the bladder diary data.

[redacted]

ALLERGAN

1839-201-021 Statistical Analysis Plan for Stage 2

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
10-Jan-2020 15:12 GMT-080	[redacted]	Biostatistics Approval
11-Jan-2020 07:23 GMT-080		Biostatistics Approval
13-Jan-2020 12:58 GMT-080		Biostatistics Approval
15-Jan-2020 08:23 GMT-080		Clinical Development Approval