STATISTICAL ANALYSIS PLAN

Protocol Number:	URO-902-2001
Protocol Title:	An Exploratory Phase 2a Study Evaluating the Efficacy and Safety of URO-902 in Subjects with Overactive Bladder and Urge Urinary Incontinence
Protocol Version and Date:	Version 3.0 (Amendment 2); 19-Feb-2021
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Indication	Overactive Bladder and Urge Urinary Incontinence
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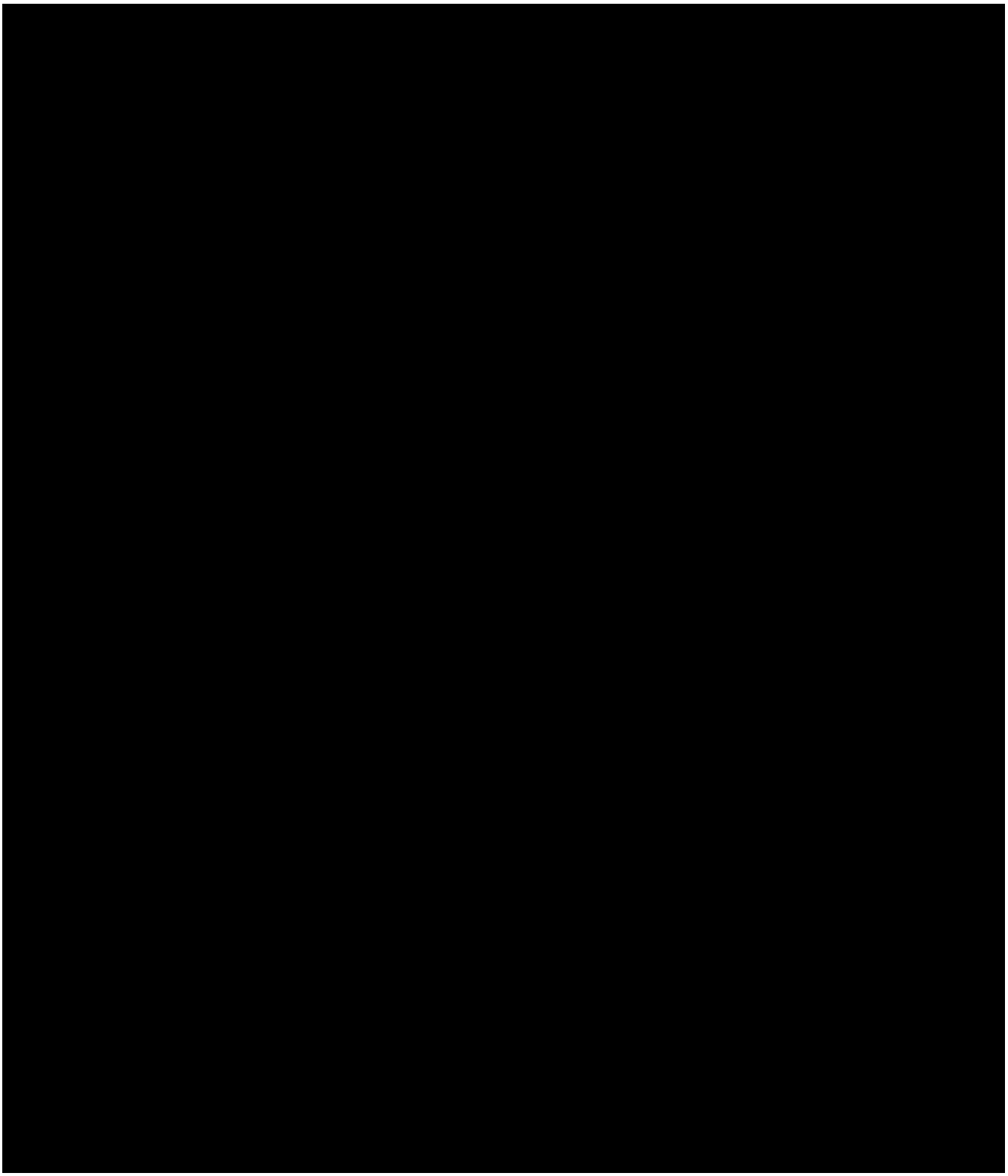

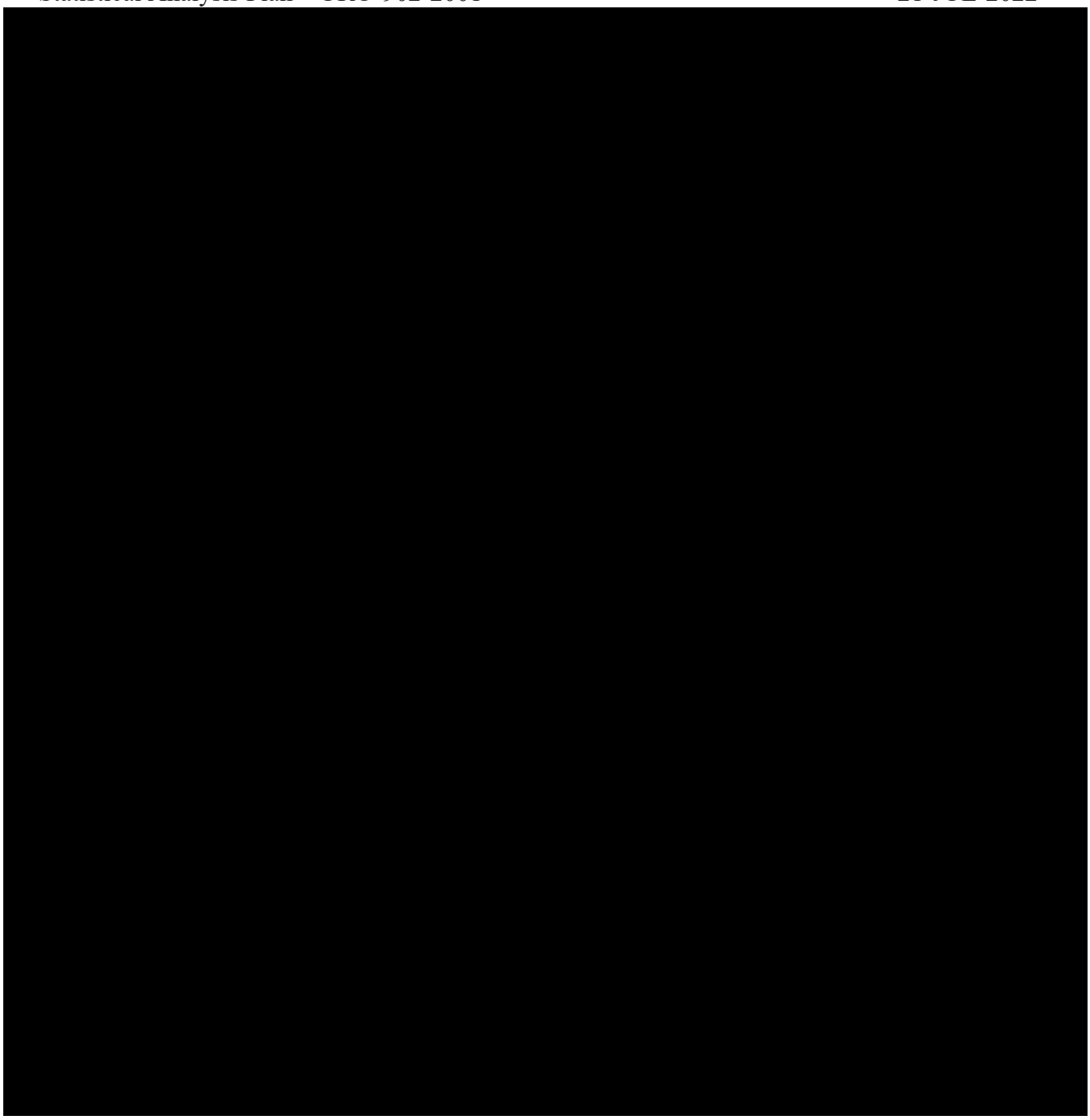

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutical Chemical
BMI	body mass index
CFB	change from baseline
CI	confidence interval
CIC	clean intermittent catheterization
CMH	Cochran-Mantel-Haenszel
CSR	clinical study report
DBP	diastolic blood pressure
DNA	double-stranded deoxyribonucleic acid
DO	detrusor overactivity
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
ED	erectile dysfunction
EDC	electronic data capture
EOS	end of study
FSV	Cystometric volume at 1st sensation to void
HRQL	health-related quality of life
IDC	involuntary detrusor contraction
I-QOL	Incontinence Quality-of-Life Instrument
ITT-E	intent-to-treat exposed
IxRS	interactive voice or web response system
LSMEANS	least squares means
MCC	maximum cystometric capacity
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
MMRM	mixed model for repeated measures
OAB	overactive bladder
$Pdet_{MaxStorage}$	maximum detrusor pressure during the storage phase
P_{det}@1stIDC	maximum detrusor pressure during the first IDC
PD	protocol deviation
PGI-C	Patient Global Impression of Change
PT	preferred term
PVR	post-void residual
REML	restricted (or residual) maximum likelihood
SAP	statistical analysis plan
SBP	systolic blood pressure

Abbreviation	Term
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment emergent adverse event
TL	topline
TLF	table, listing, and figure
UI	urinary incontinence
UUI	urge urinary incontinence
Vol@1stIDC	volume at first IDC
WHO	World Health Organization

SAP VERSION HISTORY

Version	*Date*	*Description of Changes*
1.0	**01-NOV-2021**	***Original Document***
2.0	**21-JUL-2022**	***Added second interim analysis, revise the MIC definition as well as the average Urine volume per MIC calculation***

1. INTRODUCTION

This statistical analysis plan (SAP) provides a description of the statistical methodology to be implemented for the analyses of data from Protocol Version 3.0 Amendment 2, and to be included in the clinical study report. Any deviations from this analysis plan will be documented in the final clinical study report.

There is a significant unmet need for treatment of overactive bladder (OAB) with agents with novel mechanisms of action and a well-tolerated safety profile, in particular, for patients who have been inadequately managed by pharmacologic therapy. Based on the well tolerated favorable safety profile demonstrated in the completed studies in subjects with OAB and [redacted], the current exploratory study is designed to evaluate the efficacy and safety of a single treatment of URO-902 administered via intradetrusor injection in subjects with OAB and urge urinary incontinence (UUI).

1.1. Study Objectives and Endpoints

This exploratory study has no formal statistical primary endpoint hypothesis. Study objectives and endpoints are as follows:

1.1.1. Efficacy Objectives

Efficacy Objectives	Endpoints
To evaluate the efficacy of a single dose of URO-902 24 mg and 48 mg (administered via intradetrusor injection), compared with placebo, in subjects with OAB and UUI up to 48 weeks post-dose	• Change from baseline at Week 12 in average daily number of UUI episodes • Change from baseline at Week 12 in average daily number of micturitions • Change from baseline at Week 12 in average daily number of urinary incontinence (UI) episodes • Change from baseline at Week 12 in average daily number of urgency episodes • Proportion of subjects achieving ≥ 50%, ≥ 75%, and 100% reduction from baseline at Week 12 in UUI episodes per day • Proportion of subjects achieving ≥ 50% and 100% reduction from baseline at Week 12 in number of average daily UI episodes • Change from baseline at Week 12 in average volume voided per micturition • Health outcomes parameters: o Change from baseline at Week 12 in total summary score from the Urinary Incontinence-Specific Quality-of-Life Instrument (I-QOL)

	○ Change from baseline at Week 12 in OAB Questionnaire (OAB-q) scores ○ Overall change of bladder symptoms based on the Patient Global Impression of Change (PGI-C) scale score at Week 12 • Urodynamic parameters (read by an independent central reviewer): ○ Cystometric volume at 1st sensation to void (FSV) ○ Maximum cystometric capacity (MCC) ○ Maximum detrusor pressure during the storage phase (P_{detmax}) ○ Presence/absence of the first involuntary detrusor contraction (IDC) and, if present: ▪ Volume at first IDC ($V_{PmaxIDC}$) ▪ Maximum detrusor pressure during the first IDC (P_{maxIDC}) • Change from baseline at Week 12 in average daily number of nighttime voids

1.1.2. Safety Objectives

Safety Objectives	Endpoints
To evaluate the safety and tolerability of a single dose of URO-902 24 mg and 48 mg (administered via intradetrusor injection), compared with placebo, in subjects with OAB and UUI up to 48 weeks post-dose	Safety endpoints include adverse events, serious adverse events, physical examination, vital signs (pulse rate, blood pressure, respiration rate, and body temperature), hematology and clinical chemistry, post-void residual (PVR) urine volume, electrocardiograms (ECGs), concomitant medications and concurrent procedures.

1.1.3. Other Objectives

Other Efficacy Objectives	Endpoints
Other endpoints include hSlo cDNA concentrations (blood and urine).	• Proportion of subjects with detectable hSlo cDNA concentrations • Summary of mean hSlo cDNA concentrations

1.2. Study Design

1.2.1. Overall Study Design

This is a multicenter, randomized, double-blind, placebo-controlled, single-treatment, 2-cohort, dose-escalation study.

URO-902 24 mg will be administered as intradetrusor injections to subjects in Cohort 1. An independent Data and Safety Monitoring Board (DSMB) will make the recommendation

regarding dose escalation only after unblinded review of safety data once all subjects in Cohort 1 reach Week 6 (or prematurely discontinue). Randomization at the higher dose (URO-902 48 mg) will begin only after the DSMB has recommended it is safe to proceed to Cohort 2

- Cohort 1: URO-902 24 mg and matching placebo
- Cohort 2: URO-902 48 mg and matching placebo

An estimated total of 78 subjects will be enrolled into 2 cohorts with approximately 39 subjects randomized into each cohort. In both cohorts, subjects will be randomized in a 2:1 ratio to receive either URO-902 (24 mg or 48 mg) or placebo. Each cohort will be randomized separately, and enrollment will be sequential, starting with Cohort 1 (URO-902 24 mg [n = 26] and placebo [n = 13]) and followed by Cohort 2 (URO-902 48 mg [n = 26] and placebo [n = 13]).

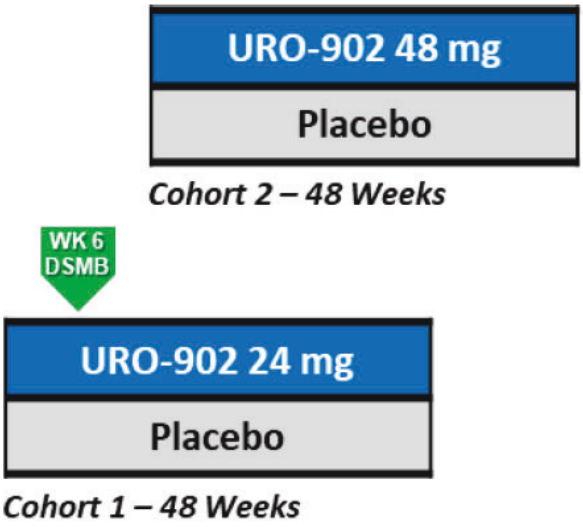
Prior to protocol amendment 1, subjects in Cohort 1 were randomized based on two stratification factors: baseline UUI episodes per day (≤3 vs. >3 UUI episodes per day), and presence and absence of detrusor overactivity (DO). Post-protocol amendment 1, subjects were randomized based on a new randomization scheme and presence or absence of DO was replaced with prior onabotulinumtoxinA use. All subjects randomized prior to and post amendment 1 will have the baseline UUI episodes per day as a stratification factor. The subjects randomized under the original randomization scheme will be considered Cohort 1a and subjects randomized under the new randomization scheme will be considered Cohort 1b. For reporting purposes, Cohort 1a and Cohort 1b will be combined and subjects enrolled in Cohort 1a will be considered onabotulinumtoxinA naïve.

Study visits will be identical for Cohorts 1 and 2. Subjects will be evaluated during a 5-week screening and randomization period for eligibility (Days -35 to -1). Eligible subjects will be randomized to treatment at the Randomization Visit (Visit 2) within each cohort; however, subjects will be administered the study treatment via cystoscopy on Day 1 (Visit 3). All subjects will be evaluated at scheduled post-treatment clinic visits at Weeks 2, 6, 12, 18, and 24 (Visits 4 to 8, respectively), or until the subject exits the study. Week 18 may be conducted by phone or other virtual technology. Afterwards, 2 follow-up visits by phone or other virtual technology will be performed at Week 36 (Visit 9) and Week 48 (Visit 10) for subjects who have completed the Week 24 Visit.

Starting at Week 24 (Visit 8), subjects can request and receive additional OAB treatment(s) at the clinical discretion of the investigator. Subjects who receive additional OAB treatment(s) at Week 24 or after will only be followed to assess adverse events at any future telephone (or other virtual technology) visits (Week 36 and/or Week 48). No bladder diaries will be collected, and no efficacy assessments will be performed once a subject receives an additional OAB treatment.

Refer to Section 1.3 of the protocol for a detailed time and events schedule. Study schema is shown below:

Figure 1: Schematic of Study Design: 2-Cohort, Dose-Escalation



1.2.2. Randomization and Blinding

Randomization will occur centrally using an interactive voice or web response system (IxRS) using central, stratified block randomization. Randomization will be done separately for Cohort 1 and Cohort 2 and will be stratified based on the following stratification factors:

- Baseline UUI episodes per day (≤ 3 vs. > 3), and
- Prior onabotulinumtoxinA use (naïve vs. prior use)

As mentioned in the previous section, subjects enrolled under the randomization scheme prior to protocol amendment 1 (Cohort 1a) will be considered onabotulinumtoxinA naïve when combined with Cohort 1b for analyses and summaries.

To maintain blinding of the treatment groups, neither the investigator/physician subinvestigator (injector) nor site personnel who are involved in evaluating or injecting the subject should prepare the study drug. An additional individual (eg, unblinded pharmacist or nurse) with no subject evaluation or treatment involvement must be identified at each investigative site to prepare the study drug and the PBS-20% flushing solution. The responsibility of this individual will be to properly prepare the injection syringes with the accurate randomized study drug as per the volumes indicated by the Sponsor. They will draw the study drug into the syringes to be injected and dilute as needed as per instructions in the study manual.

For the interim analysis(es), the subject and the investigator or delegate(s) who are involved in the treatment or clinical evaluation of the subjects will remain blinded to the treatment assignments. Limited personnel from the Sponsor will be unblinded (double-blind, sponsor-

open design). Sponsor personnel/designees who are directly involved with site interactions and communications (eg, study operations lead and site monitors) will remain blinded to subject level treatment assignment.

1.2.3. Statistical Hypotheses

The study has no formal statistical primary endpoint hypothesis. The intent is to estimate the treatment effect of each dose group relative to placebo. For the final analysis, the subjects receiving placebo from Cohort 1 and Cohort 2 will be pooled.

1.2.4. Sample Size Justification

For this exploratory study, the sample size was empirically chosen. With a total of 23 evaluable female subjects in each of the URO-902 treatment groups and 23 evaluable female subjects in the placebo group, this study would have approximately 55% power to detect a between-group difference of 1.8 episodes in the mean change from baseline to Week 12 in the number of UUI episodes per day between the URO-902 and placebo treatment groups (based on a 2-sample t-test with a 2-sided type I error rate of 0.05 and standard deviation [SD] of 2.86). Furthermore, the half-width of the confidence interval would be the following for different SD assumptions:

Table 1: Sample Size Determination Parameters

SD	N per Group	Half-Width of Confidence Interval	Lower Limit	Upper Limit
2.86	23	1.70	0.10	3.50
3.00	23	1.78	0.02	3.58
2.55	23	1.49	0.31	3.29

In order to account for subject attrition (approximately 10%), the sample size was increased to 26 subjects for each treatment group, amounting to a total of 78 randomized subjects required for exploratory efficacy analyses in both Cohort 1 (n = 39) and Cohort 2 (n = 39).

2. PLANNED ANALYSES

2.1. Interim Analysis

Two or more interim analyses may be conducted; when ≥ 50% of subjects in Cohort 1, and/or when ≥ 50% of subjects in Cohort 2 have completed at least 12 weeks of follow-up post-treatment administration (or prematurely exited the study prior to Week 12). Any interim analysis performed is for future planning purposes and no adjustment to the type I error will be made.

The planned interim analysis will be conducted to evaluate the objectives of the protocol at Week 12. These analyses will be performed after the completion of the following steps:

- All subjects in Cohorts 1 and 2 have completed Week 12 (or prematurely exited the study prior to Week 12).

- All required database cleaning activities have been completed and final database release and freeze has been declared by data management for all subjects to be included in the interim analysis.

- All criteria for unblinding the randomization code have been met.

Similar to the planned Week 12 interim analysis, a second planned interim analysis will be conducted after all subjects complete Week 24 (or prematurely exited the study prior to Week 24). This analysis will evaluate the objectives of the protocol at Week 24.

2.2. Final Analysis

The [redacted] will perform the production and quality control of all tables, figures and listings on behalf of Urovant Sciences, Inc.

Statistical programming will start after data have been collected and are available in the database. Blinded dry-runs using dummy treatment code will be performed prior to database lock and unblinding to ensure programming displays and algorithms are developed as planned. The planned final end-of-study analysis will be performed once the final clinical database lock (after all subjects complete the study or exit the study prematurely) has been achieved and treatment codes have been unblinded to the statistics and programming team. The clinical study report will be based on final analysis results.

2.3. Data and Safety Monitoring Board

A DSMB will be retained to assess, on an ongoing basis, all safety aspects of this study including unblinded review of safety data after all subjects reach Week 6 (or prematurely discontinue) in Cohort 1 (URO-902 24 mg). Randomization at the higher dose (URO-902 48 mg) will begin only after the DSMB has recommended it is safe to proceed to Cohort 2. This committee will be an external independent DSMB that monitors safety. The detailed activities including meeting plans will be described and documented in the DSMB Charter. A separate statistical analysis plan may be prepared for the DSMB.

3. ANALYSIS POPULATION

3.1. Analysis Population

3.1.1. Screened Population

The screened population consists of all subjects who are screened for the study. This population is used primarily for subject accounting purposes and will generally not be used for summary or analysis.

3.1.2. Randomized Population

The randomized population consists of all subjects who are randomized to receive any double-blind study drug regardless of whether they received the study drug.

3.1.3. Safety Population

The safety population consists of all subjects from Cohorts 1 and 2 who were randomized and received study drug and will be used to analyze all safety endpoints based on actual treatment received.

3.1.4. Intent-to-treat Exposed (ITT-E)

The ITT-E population consists of all subjects who are randomized and treated from Cohorts 1 and 2. ITT-E will be used for demographics, baseline characteristics, and efficacy analyses. Subjects will be included in the treatment group to which they are randomized.

3.2. Violations and Deviation

Subjects who do not meet eligibility criteria but are still randomized will be analyzed according to the analysis population described in Section 3.1.

3.2.1. Protocol Deviations

The final list of major protocol deviations will be finalized and documented prior to database lock except for the deviation category of wrong treatment which will be confirmed upon study unblinding. Only major protocol deviations will be summarized and listed in the Clinical Study Report (CSR). Major deviations will be those which are considered to potentially impact upon the interpretation of the primary efficacy endpoint in the study or may potentially impact the interpretation of safety. Major protocol deviation categories may include, but are not limited to the following:

- Randomized subjects who do not meet the inclusion criteria
- Randomized subjects who meet any of the exclusion criteria
- Subjects who received the wrong treatment

- Concomitant use of prohibited medications not approved by the medical monitor
- Randomized subjects who met withdrawal criteria during the study but were not withdrawn

Due to the limited sample size of the study, no sensitivity analysis will be performed on a per-protocol population.

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. General Principles for Data Analysis

The general formats and layouts of tables, listings, and figures (TLFs) are provided in a separate "programming consideration" document. Actual formats and layouts may be altered slightly to accommodate actual data or statistics. Minor format changes will not require updates to the SAP.

The TLF numbering and general content follow the ICH E3 guidelines.

4.1.1. Multicenter Study

In this study the stratified permuted block randomization is not done within centers. The analyses will be conducted by pooling data from all study centers and will not include study center as a covariate in the statistical modeling.

4.1.2. Testing Strategy and Multiplicity Adjustments

No formal multiplicity adjustment will be performed. Nominal p-values will be provided for all exploratory efficacy analysis as a measure of the strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses.

4.1.3. Examination of Subgroups

To determine whether the treatment effect is consistent across various subgroups, the efficacy endpoints related to UUI, micturitions, UI, and urgency episodes will be summarized descriptively for each of the following subgroups:

- Baseline UUI episodes per day (≤3 vs >3)
- Presence or absence of DO
- Previous use of onabotulinumtoxinA (naïve vs. prior use)

Baseline UUI episodes per day will be based on the actual value collected at baseline, presence or absence of DO will be based on the central reader's assessment on the urodynamics form, and prior onabotulinumtoxinA use will be based on the randomization stratification from the new randomization scheme after the amendment 1. The subjects enrolled in Cohort 1a will be considered onabotulinumtoxinA naïve.

4.2. General Data Handling Conventions

4.2.1. Study Treatment Description

Randomized treatment groups will be displayed as shown in the following table:

Data Displays for Reporting	
Description	Order in TLF
Placebo	1
URO-902 24 mg	2
URO-902 48 mg	3
Overall (if applicable)	4

For the reporting done within each cohort, the treatment group applicable to the cohort will be used in the output (i.e. URO-902 24 mg for Cohort 1 and URO-902 48 mg for Cohort 2).

4.2.2. Reporting Conventions

General rules

In general, all collected safety data, any derived efficacy parameters from the bladder diary, questionnaire data, and urodynamic data will be presented in subject data listings. Listings will be ordered by treatment, subject number, and assessment week or event date. The treatment group presented in listings will be based on the planned assignment for efficacy endpoints and actual assignment for safety endpoints.

Summary tables will be provided for all randomized subjects. All demographic and baseline data will be presented by treatment arm and overall, unless otherwise specified. Bladder diary, questionnaire, urodynamic data, and safety data will be presented by treatment arm only. In general, continuous variables will be summarized to include the population sample size (N), number of subjects with available data (n), arithmetic mean, standard deviation (SD), median, minimum, Q1, Q3 and maximum values. Categorical variables will be summarized by the population size (N), number of subjects with available data (n), number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data (n) in the analysis set of interest. Selective ordinal data may be summarized using both descriptive statistics as well as counts and percentages of subjects in each category, as appropriate.

The data analyses will be conducted using the SAS® System (SAS Institute Inc., Cary, NC) version 9.3 or above. The eClinical Solutions' standard operating procedures will be followed for the validation of all SAS programs and outputs.

Formats

Numeric data will be reported at the precision collected on the electronic case report form (eCRF). The reported precision from non eCRF sources may be adjusted to a clinically interpretable number or decimal places.

Unscheduled Visits

Unscheduled visits will be assigned to an analysis visit using the all-inclusive windows defined in Section 4.2.4. If multiple assessments are done in the same visit, the selection rule in Section 4.2.4 will apply. All assessments at unscheduled visits will be included for deriving last post-baseline or maximum value post-baseline and in the data listings.

4.2.3. Premature Withdrawal and Missing Data

If any missing data are present in diary data for any reasons, no imputation will be applied to derive responder. No explicit missing data imputation will be performed for change from baseline since a mixed model for repeated measures (MMRM) will be applied to change from baseline analysis. For responder analyses, subjects with missing assessments will be considered non-responders. Missing items from the questionnaires will be handled according to the respective measure instructions as described in Section 4.3.3.

In general, missing safety data will not be imputed and only observed values will be analyzed.

If the relationship of an AE record ("Relationship to Study Treatment" on AE eCRF) is missing this AE will be considered "Probably Related" to the study treatment. If the AE severity is missing every effort should be made to acquire the information from the investigator. "Severe" will be assigned to a missing intensity for reporting purposes.

The general imputation rules of partial missing date for both AE and concomitant medication are detailed below:

Dates with missing the day of the year will adhere to the following conventions:

- The missing day of onset date will be set to:
  - First day of the month that the event occurred, if the onset YYYY-MM is after the YYYY-MM of the study treatment
  - The day of the study treatment, if the onset YYYY-MM is the same as YYYY-MM of the study treatment

  - The date of informed consent, if the onset YYYY-MM is before the YYYY-MM of the study treatment.

- The missing day of end date will be set to:

  - The last day of the month of the occurrence. If the subject died in the same month, then set the imputed date as the death date.

Dates with missing both the day and month of the year will adhere to the following conventions:

- Missing day and month of onset date will be set to:

  - January 1 of the year of the onset, if the onset YYYY is after the YYYY of the study treatment

  - The date of the study treatment, if the onset YYYY is the same as YYYY of the study treatment

  - The date of informed consent, if the onset YYYY is before YYYY of the study treatment

- The missing date of end date will be set to:

  - December 31 of the year of occurrence. If the subject died in the same year, then set the imputed date as the death date.

4.2.4. Analysis Visiting Windows

No analysis visit window will be defined for urodynamic data, and questionnaire data. Nominal clinical visits will be used for summary and analysis. Any unscheduled data will be listed only.

Diary data used for analyses will be windowed as follows:

1. For baseline, the 3-day diary completed closest to study drug administration will be used regardless of when the diary is completed within the screening and randomization period.

2. For post-baseline the analysis visit windowing will be based on the scheduled visit dates relative to the study drug administration date according to the schedule of assessments in the protocol instead of the actual visit dates. This is set up to take into account the visit delays due to COVID-19 should it happen. Table below provides details on the target study day and corresponding visit windowing rules for the post-baseline visits.

Table 2: Diary Data Analysis Visit Window Slotting

Analysis Visit	Target Study Day	Range	Visit Window
Week 2	15	15 ± 7 days	[8, 22]
Week 6	43	43 ± 14 days	[29, 57]
Week 12	85	85 ± 14 days	[71, 99]
Week 18	127	127 ± 14 days	[113, 141]
Week 24	169	169 ± 14 days	[155, 183]
Week 36	253	253 ± 21 days	[232, 274]
Week 48	337	337 ± 21 days	[316, 358]

For safety endpoints such as vital signs, laboratory tests, PVR, and ECGs, data records will be slotted to one of the protocol specified visits using the analysis visit window rules below:

After all the records have been assigned to an analysis visit, if there are more than one records in the same analysis visit, the one closest to the target day will be used (for records in screening and randomization visits, the later one will be selected). If equal distance, the earlier one will be used. If there are more than one results in the same day, the time portion of the collection date and time, the “repeat” status, or the inherent sequence in the electronic data capture (EDC) system will be used for differentiation and the later one will be used.

Table 3: Analysis Visit Window Slotting

Analysis Window Label	Nominal Visit	Nominal Day	Visit Window
Screening	Screening Visit	Not Applicable	Not Applicable
Randomization	Randomization Visit	Not Applicable	Not Applicable
Day 1	Day 1	1	Not Applicable
Week 2	Week 2	15	VS, PVR: [2, 29] ECG: [2, 50]
Week 6	Week 6	43	VS, PVR: [30, 64] Lab: [1, 106]
Week 12	Week 12	85	VS, PVR: [65, 106] ECG: [51, 127]
Week 18	Week 18	127	VS, PVR: [107, 148]
Week 24	Week 24	169	VS, PVR: 149+ ECG: 128+ Lab: 107+

4.3. Data Definitions and Deviations

4.3.1. Efficacy Data Collection Schedule

Efficacy assessments will be collected as outlined in Table 4 below. Refer to protocol section 1.3 (Schedule of Assessments) for the details on the day of visit and timing of measurement.

Table 4: Efficacy Assessments

Assessment	Form	Measurement and Timing
Bladder Diary	Bladder Diary – Day 1 Bladder Diary – Day 2 Bladder Diary – Day 3 eCRF form	For any 3 consecutive days within the Screening and Randomization period (Visits 1 and 2) and any 3 consecutive days in the 7 days prior to the clinical visit (Weeks 2, 6, 12, 18, 24, 36, and 48 (Visits 4-10, respectively)), subjects will record daily urination data including “Need to urinate immediately” “Urinated in toilet” “Accidental urine leakage” “Main reason for leakage” For one 24-hour period, subject will also record the urine volume for one of the diary days

Assessment	Form	Measurement and Timing
Health Outcome parameters	• Incontinence Quality of Life Instrument (I-QOL) eCRF • Overactive Bladder Questionnaire (OAB-q) eCRF • Patient Global Impression of Change Scale (PGI-C) eCRF	• I-QOL: Day 1, Weeks 6, 12 • OAB-q: Day 1, Weeks 6, 12 • PGI-C: Week 12
Urodynamics	Urodynamics – Site Urodynamics – Central Reader	Prior to Randomization at Visit 2 and Week 12

4.3.2. Bladder Diary Data

Bladder Diary data are collected following the schedule of assessments in Section 1.3 of the protocol. Per protocol diaries will not be collected if subjects receive additional OAB treatment(s) at Week 24 or after. For summary and analysis purpose, any bladder diaries collected after the first additional OAB treatment will not be included in defining the subsequent endpoints based on the bladder diaries. All bladder diaries collected will be included in the listings.

4.3.2.1. Average Daily Number of UUI Episodes

Average daily number of UUI episodes is calculated as the total number of UUI episodes recorded on the bladder diary days that fall within the visit window divided by the number of days the Bladder Diary is filled out. A UUI episode is defined as when a subject checked "Urge" to the question "select main reason for leakage" on the bladder diary eCRF. Subjects may have more than one bladder diary filled out on the same day and all the UUI episodes will be summed together. The denominator used for calculating the average number will only count the days in which there is a completed bladder diary day within the visit window.

4.3.2.2. Average Daily Number of Micturitions

Average daily number of micturitions is defined as the total number of times a subject checked "Urinated in toilet" or recorded non-zero urine volume in a completed bladder diary day within the visit window divided by the number of days the Bladder Diary is filled out. Subjects may have more than one bladder diary filled out on the same day and all the micturitions will be summed together. The denominator used for calculating the average number will only count the days in which there is a completed bladder diary day within the visit window.

4.3.2.3. Average Daily Number of UI Episodes

Average daily number of UI episodes is calculated as the total number of UI episodes recorded on a completed diary day within the visit window divided by the number of days the Bladder Diary is filled out. A UI episode is defined as when a subject answered "Yes" to the question "Accidental urine leakage" or indicates any reason for leakage on the bladder diary eCRF.

Subjects may have more than one bladder diary filled out on the same day and all the UI episodes will be summed together. The denominator used for calculating the average number will only count the days in which there is at least one completed bladder diary day within the visit window.

4.3.2.4. Average Daily Number of Urgency Episodes

Average daily number of urgency episodes is calculated as the total number of urgency episodes recorded on a completed diary day within the visit window divided by the number of days the Bladder Diary is filled out. An urgency episode is defined as when a subject answered "Yes" to the question "Need to urinate immediately" on the bladder diary eCRF. Subjects may have more than one bladder diary filled out on the same day and all the urgency episodes will be summed together. The denominator used for calculating the average number will only count the days in which there is at least one completed bladder diary day within the visit window.

4.3.2.5. Proportion of Subjects Achieving ≥ 50%, ≥ 75%, and 100% Reduction from Baseline at Week 12 in UUI Episodes per Day

Proportion of subjects achieving x% reduction from baseline is defined as: - (Average daily number of UUI episodes at Week n – UUI at Baseline) / UUI at Baseline * 100%. This is defined when both baseline and post-baseline average daily number of UUI episodes are non-missing. For responder analyses, missing reduction from baseline will be considered non-responders for the visit in question.

4.3.2.6. Average Volume Voided per Micturition

A subject is expected to fill out the volume voided for one 24-hour period during the 3-day diary collection window. The average volume voided per micturition is calculated as the arithmetic mean of all voids for which a subject has recorded a positive volume, even if volume voided is filled out for more than one 24-hour period.

4.3.2.7. Average Daily Number of Nighttime Voids

Average daily number of nighttime voids is defined as the total number of times a subject checked "Urinated in toilet" or recorded non-zero urine volume in a completed bladder diary day within the visit window between the hours of 11:00 PM and 6:00 AM the following day, divided by the number of days the Bladder Diary is filled out. Subjects may have more than one bladder diary filled out on the same day and all the nighttime voids will be summed together. The denominator used for calculating the average number will only count the days in which there is at least one completed bladder diary day within the visit window.

4.3.2.8. Proportion of Subjects Achieving ≥ 50% and 100% Reduction from baseline in Number of Average Daily UI Episodes

Proportion of subjects achieving x% reduction from baseline is defined as: - (Average daily number of UI episodes at Week n – UI at Baseline) / UI at Baseline * 100%. This is defined when both baseline and post-baseline average daily number of UI episodes are non-missing.

For responder analyses, missing reduction from baseline will be considered non-responders for the visit in question.

4.3.3. Questionnaires Data and Scoring

4.3.3.1. Total Summary Score from I-QOL

I-QOL is a validated, disease-specific quality of life questionnaire designed to measure the impact of urinary incontinence on patients' lives. It contains 22 items. The response options and values for each item are:

- Extremely (value = 1)
- Quite a bit (value = 2)
- Moderately (value = 3)
- A little (value = 4)
- Not at all (value = 5)

A total summary score is calculated based on the 22 items; additionally, three domain scores (Avoidance and Limiting Behavior, Psychosocial Impact, and Social Embarrassment) can be calculated based on responses to items corresponding to each respective domain. The score will only be derived when at least 50% of the items are completed: i.e. ≥ 11 items are completed at one visit [1]. The three domains will be considered missing if the total score is missing. The three domains include the following items:

Table 5: I-QOL Scoring

Domain	Items	Lowest Possible Scores	Possible Range
Total Summary Score	1 to 22	22	88
Avoidance and Limiting Behavior	1, 2, 3, 4, 10, 11, 13, 20	8	32
Psychosocial Impact	5, 6, 7, 9, 15, 16, 17, 21, 22	9	36
Social Embarrassment	8, 12, 14, 18, 19	5	20

The total score and each domain score are based on the transformation of the raw score to a 0 to 100 scale using the formula below:

$$= \frac{sum\ of\ the\ items - lowest\ possible\ score}{possible\ raw\ score\ range} \times 100$$

The higher score corresponds to a better quality of life.

Subjects who had at least a 10-point increase of I-QOL total summary score from baseline to post-baseline visits are considered responders who achieved the minimally important difference (MID). Subjects who had an increase less than 10 points at any post-baseline or change from baseline is missing are considered non-responders.

4.3.3.2. OAB-q Scores

The OAB-q was developed to assess symptom bother and the impact of OAB on health-related quality of life (HRQL). It contains 33 items and the response options and values for each item are:

- Not at all / None of the time (value = 1)
- A little bit / A little of the time (value = 2)
- Somewhat / Some of the time (value = 3)
- Quite a bit / A good bit of the time (value = 4)
- A great deal / Most of the time (value = 5)
- A very great deal / All the time (value = 6).

The instrument yields a HRQL total score and four subscales as listed in the table below:

Table 6: OAB-q Scoring

Scale	Items	Lowest, Highest Possible Scores	Possible Range
Total HRQL	9 to 33	25, 150	125
Symptom Bother	1 to 8	8, 48	40
Coping	9, 11, 16, 21, 22, 26, 32, 33	8, 48	40
Concern	12, 13, 14, 19, 23, 25, 29	7, 42	35
Sleep	10, 15, 24, 17, 30	5, 30	25
Social Interaction	18, 20, 27, 28, 31	5, 30	25

For the Symptom Bother Score, the transformed score is:

$$= \frac{sum\ of\ the\ items - lowest\ possible\ score}{possible\ raw\ score\ range} \times 100$$

The higher score corresponds to a larger bother.

For Coping, Concern, Sleep, Social Interaction, and Total HRQL scores, the score is:

$$= \frac{highest\ possible\ score - sum\ of\ the\ items}{possible\ raw\ score\ range} \times 100$$

The higher score corresponds to a higher quality of life.

If < 50% of the scale items are missing, the scale will be retained with the mean scale of the items present used to impute a score for the missing items. If ≥ 50% of the items are missing, no scale score will be calculated, the subscale score should be considered missing [2].

4.3.3.3. PGI-C Scale Score

The PGI scale in this study is an OAB-specific quality of life questionnaire. The tool was designed to assess the impact (and improvement) of urinary incontinence on activities of daily living, wellbeing, and function. The eCRF collects PGI severity, control, frequency, leakage, as well as change. All PGI scales are ordinal assessments going from lower impact of disease to highest impact of disease. PGI-Severity ranges from 1 to 4, PGI-Control, PGI-Frequency, PGI-Leakage range from 1 to 5. PGI-Change ranges from 1 to 7. These questions will be displayed as categorical variables with count and percent for each category at Week 12. Also, PGI-Change will be analyzed as a dichotomous responder variable. Subjects who answer "Much better" or "Moderately better" will be considered responders, while all other answers and missing values will be considered non-responders.

4.3.4. Study Day and Duration

Study day is relative to the start date of the double-blind treatment. This is used to describe the relative time of an event or assessment that happened during the study. The first day of the study is defined as the day a subject receives either URO-902 (24 or 48 mg) or placebo. There is no study Day 0 defined.

- For an event or assessment that occurred on or after the study treatment: Study day = Date of event or examination – date of study treatment + 1
- For an event or assessment that occurred prior to the study treatment: Study day = Date of event or examination – date of study treatment

A duration between any two dates (such as AE duration) expressed in days will be calculated using the following conventions: Duration = later date – earlier date + 1.

4.3.5. Baseline and Change from Baseline

In general, the last recorded value prior to the study treatment will serve as the baseline measurement for the safety endpoints such as lab, vital signs, and ECGs. For numeric result, the mean of the multiple values will be used as baseline if multiple measurements are collected on the same baseline day without the time or "repeat" status to differentiate the records. For categorical results, the record with the later sequence number or collection time will be used if multiple measurements are collected on the same baseline day. For the bladder diary data, the 3

diary days collected during the screening and randomization period and closest to the treatment administration is considered baseline. All 3 diary days are required for the change from baseline derivation. For the questionnaires, the baseline is the data collected on the Day 1 Visit prior to treatment.

Change from baseline will be calculated as the post-baseline value minus the baseline value. Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100. If either the baseline or post-baseline value is missing, then change from baseline and percentage change from baseline will be set to missing.

5. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

5.1. Subject Disposition and Withdrawals

Subject disposition will be summarized for Screened population and by treatment group for the Randomized population separately. The summary for the screened population will include number of subjects who passed screening and who were screen failures and corresponding screen failure reasons.

For the disposition summary of the randomized population, the following categories will be presented; randomized, completed Week 24, completed Week 48 follow-up, withdrawn from study (and reason), received study treatment, did not receive any treatment, additional OAB treatment prescribed.

Reasons for exclusion from analysis population will also be summarized based on the populations defined in Section 3.1.

The frequency and percentage of subjects with at least one major Protocol Deviation (PD), major PD by classification and reasons/category for PD will be summarized by treatment arm for the Randomized population.

Eligibility criteria, screen failures (including date and primary reason for failure), and informed consent (protocol version, informed consent version date and date signed) will be listed for all subjects screened.

A summary of randomized subjects by investigator name and site identification will be provided.

Randomization details will also be listed, including the date of randomization, randomization number and randomization strata.

5.2. Demographic and Baseline Characteristics

All demographic and baseline characteristic data will be summarized by treatment group using descriptive statistics for all subjects in the ITT-E population.

The summary table will include age, age category (<65, ≥65 years), ethnicity, race, baseline UUI episodes per day (<=3, >3) (as randomized and actual baseline), presence or absence of DO (site and central assessments), previous use of onabotulinumtoxinA (naïve vs. prior use) (as randomized and actual baseline), weight, height and body mass index (BMI).

The actual baseline for UUI episodes per day is derived based on the logic described in Section 4.3.2.1. The actual previous use of onabotulinumtoxinA status is based on searching for the preferred term of "BOTULINUM TOXIN TYPE A" in subject's medications taken before randomization.

Age (years), height (cm), weight (kg), and BMI (kg/m^2) captured at Screening will be summarized as a continuous variable.

All demographic data will be listed.

5.3. Medical History and Concomitant Disease

Descriptions of medical history findings will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher.

A disease or illness reported as medical history without a start date will be included in medical history without a date assigned. Medical history will be sorted by descending overall frequency, by system organ class (SOC) and preferred term (PT) in the summary table. Medical history data listings will be sorted by treatment, subject number, start date, SOC and PT.

5.4. Prior and Concomitant Medication

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug B3-Sept Format, 2019 version. These medications will be further classified as follows.

- Prior medication is defined as those medications that started prior to the study treatment.
- Concomitant medication is defined as those taken on or after the study treatment. If medications started prior to the study treatment and were ongoing after the study treatment, those medication will be considered as concomitant medication as well.

The number and percentage of subjects taking prior and concomitant medications will be summarized overall by Anatomical Therapeutical Chemical (ATC) Levels 2 and 4 for all subjects in the safety population. Prior and concomitant medications will be listed for all subjects in the safety population.

5.4.1. Additional OAB Treatment

Starting at Week 24 and after (at clinic visit, phone visits or between visits), subjects can request and be prescribed additional OAB treatment(s). A treatment is considered additional OAB treatment if on the "Concomitant Medications/Procedures" eCRF the answer to "Is this an additional OAB medication" is "Yes", regardless of when the additional OAB treatment was received.

The additional OAB medication will be summarized by ATC level 2, 4, and Preferred Term while additional OAB procedures will be summarized by preferred term. Separate listings for additional OAB medications and procedures will be provided.

6. EFFICACY ANALYSIS

In general, the ITT-E will be used for all analyses of efficacy endpoints unless stated otherwise.

6.1. Continuous Efficacy Endpoints

For continuous efficacy endpoints, the by-visit means and SD, as well as change from baseline estimated with least squares means, standard error, and 95% confidence intervals (CI) will be presented for each treatment group and the difference between each dose group relative to placebo. Nominal p-values from comparisons from each dose group relative to placebo will be provided for descriptive purposes. The change from baseline will be analyzed by a mixed model for repeated measures (MMRM) with restricted maximum likelihood estimation incorporating all applicable post-baseline visits. For average daily number of urge urinary incontinence (UUI) episodes, the MMRM model will include terms for treatment, visit, visit by treatment interaction term, baseline value, and previous use of onabotulinumtoxinA as randomized (naïve vs. prior use). For the other endpoints, one additional term of baseline UUI episodes per day category as randomized (≤ 3 vs. > 3) will be included in the MMRM model. If any of the stratification factors has a stratum with number of subjects less than 5, the factor in question will not be included in the MMRM model. If >15% of the subjects were incorrectly stratified based on the actual baseline UUI episodes per day and previous use of onabotulinumtoxinA, a sensitivity analysis using the same MMRM model but with actual values of the two stratification factors as covariates will be carried out.

The Kenward-Roger adjustment will be used with restricted (or residual) maximum likelihood (REML) to make statistical inference. An unstructured covariance matrix will be used to model the correlation among repeated measurements. If the unstructured covariance model fails to converge with the default Newton-Raphson algorithm, the Fisher scoring algorithm will be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yield convergence, the following structures will be investigated: heterogeneous Toeplitz, Toeplitz, heterogeneous First-Order Autoregressive [AR (1)],

heterogeneous compound symmetry (HCS), and compound symmetry (CS). The covariance structure converging to the best fit, as determined by Akaike's information criterion (AIC), will be used.

Results will be presented in terms of least square means (LSMEANS), treatment differences in LSMEANS, nominal p-value and 95% confidence intervals for the treatment difference for all timepoints. Type III p-values for all factors in the MMRM model will be listed on the table.

An example of the SAS code for the base procedure is given below:

```
proc mixed data = datain method = reml;
      class subject treatment visit UUI_cat onabA_use;
      model CFB = treatment visit treatment*visit baseline UUI_cat onabA_use;
                  /ddfm=KR solution chisq;
      repeated visit / subject=subject type=UN r rcorr;
      lsmeans treatment*visit / pdiff=all cl alpha=0.05;
run;
```

The normality assumptions for the primary analysis model will be assessed by inspection of the residuals from the model and normal probability plots. If assumptions of normality are grossly violated, additional supportive analysis of the data will be performed in order to assess the robustness of the conclusions drawn from the primary analysis.

Sensitivity analyses using analysis of covariance (ANCOVA) will be carried out for change from baseline at Week 12 in average daily number of UUI episodes and micturitions. The model will use the change from baseline data at Week 12 and include treatment arms and baseline value as covariates.

The following efficacy endpoints will be summarized and analyzed in this fashion (Data for all visits will also be presented):

- Change from baseline at Week 12 in average daily number of UUI episodes
- Change from baseline at Week 12 in average daily number of micturitions
- Change from baseline at Week 12 in average daily number of UI episodes
- Change from baseline at Week 12 in average daily number of urgency episodes
- Change from baseline at Week 12 in average volume voided per micturition

- Change from baseline at Week 12 in total summary score from I-QOL
- Change from baseline at Week 12 in OAB-q scores
- Change from baseline at Week 12 in average daily number of nighttime voids

For all domains and subscales in I-QOL and OAB-q the mean value and change from baseline will be summarized by visit.

6.2. Categorical Endpoints

The following categorical endpoints are included in this study (Data for all visits will also be presented)

- Proportion of subjects who has ≥ 50% reduction from baseline in UUI episodes at Week 12
- Proportion of subjects who has ≥ 75% reduction from baseline in UUI episodes at Week 12
- Proportion of subjects who has 100% reduction from baseline in UUI episodes at Week 12
- Proportion of subjects who has ≥ 50% reduction from baseline in average daily number of UI episodes at Week 12
- Proportion of subjects who has ≥ 75% reduction from baseline in average daily number of UI episodes at Week 12
- Proportion of subjects who has 100% reduction from baseline in average daily number of UI episodes at Week 12
- Proportion of responders (subjects who achieve MID for I-QOL total score) at Week 6 and 12
- Proportion of responders based on the PGI-C scale score at Week 12

The Cochran-Mantel-Haenszel (CMH) common risk difference estimate stratified by the updated stratification factors (baseline UUI episodes per day (≤ 3 vs. > 3), and prior onabotulinumtoxinA use (naïve vs. prior use)) used during randomization with weights proposed by Greenland and Robins [3] will be used to compare the proportion of responders between the active and placebo groups. If there is a stratum for a treatment group that has 0 subjects in it, the 0 count will be replaced by 0.5 in order to prevent dividing by 0 as suggested in Greenland and Robins. The estimated common risk difference, and associated p-value and 2-sided 95% confidence interval will be tabulated.

Other PGI questions collected on the PGI form, i.e. PGI-severity, PGI-control, PGI-frequency, and PGI-leakage will be summarized with count and frequency of each response at Week 12.

6.3. Urodynamic Endpoints

For urodynamic assessments only the independent central reviewer's interpretation will be summarized. The frequency and percentage of central reader's assessment compared to the investigator's reading and descriptive summary of the results of each parameter will be provided for baseline and Week 12. The change from baseline at Week 12 will also be provided.

6.4. hSlo cDNA concentrations

The presence and absence of hSlo cDNA concentrations will be summarized at each protocol specified visit. If present, numeric results of the concentration will also be summarized at each visit.

7. SAFETY ANALYSIS

The safety population will be used for all safety analyses. Safety will be based on adverse events reporting, clinical laboratory data, ECGs, PVR, physical examinations, and vital signs. No inferential statistical testing is planned on the safety data, all data will be descriptively summarized by treatment and visit.

7.1. Extent of Exposure and Compliance

Since this is a treatment with single injection at the start of the study, no summary of exposure or compliance will be provided. A listing of study injection will be provided for all subjects in the safety population.

7.2. Adverse Events

Adverse events (AEs) will be coded using MedDRA version 22.1. or later.

All reported AEs (whether treatment emergent or not) will be included in by-subject AE listings. Sorting will be by treatment, subject, date of event, SOC, PT and then verbatim description.

An AE will be considered a treatment emergent adverse event (TEAE) if it begins or worsens in severity after initial exposure of the study treatment through 48 weeks after treatment administration or the date of the initiation of another OAB medication, investigational agent or surgical intervention, whichever occurs first. The determination of "48 weeks" will be based on the study day of the AE start date instead of the visit date of the Week 48 visit. The OAB medication will be determined based on the checkbox "Is this an additional OAB medication"

on the concomitant medication CRF. After data are collected and reviewed by the clinical team, a blinded list of investigational agents and surgical interventions will be provided to the programming team prior to database lock to determine which AEs should no longer be considered treatment emergent due to possible confounding effects. Partial AE start dates will be imputed as detailed in Section 4.2.3.

Summary tables will be based on TEAEs. The incidence of TEAEs will be presented using counts and percentages of subjects with TEAEs and tabulated by SOC and PT. SOC will be sorted in descending frequency and PT within SOC will be sorted by descending frequency based on the incidence of all subjects treated with URO-902 included in the summary. If a subject has multiple occurrences (start and stop) of an event associated with a specific SOC or PT within a SOC, a subject will only be counted once in the incidence count for the SOC or PT within SOC respectively.

An overall summary table of AEs by treatment group will be presented detailing the number and percentage of subjects, and number of events for the following categories:

- At least one TEAE;
- At least one Treatment-Related TEAE;
- At least one Grade ≥ 3 TEAE (Mild = Grade 1, Moderate = Grade 2, Severe = Grade 3, Life-Threatening = Grade 4, Death = Grade 5)
- At least one Grade ≥ 3 Treatment-Related TEAE;
- At least one Serious TEAE;
- At least one Serious Treatment-Related TEAE;
- At least one TEAE leading to Discontinuation from Study;
- At least one TEAE of Special Interest;
- At least one Treatment-Related TEAE of Special Interest

Except for all TEAEs which will be summarized by SOC and PT, the incidence of all other TEAEs by PT will be presented for the following in descending frequency based on the incidence of all subjects treated with URO-902.

- All TEAEs by SOC and PT;
- All TEAEs
- Treatment-related TEAEs (i.e., Possibly Related or Probably Related);
- All TEAEs by PT, and maximum severity (where the maximum intensity per subject will be counted at each level of summarization);
- TEAEs with Grade ≥ 3;

- Treatment-related TEAEs with Grade ≥ 3;
- Serious TEAEs;
- Treatment-related serious TEAEs;
- Fatal TEAE;
- TEAEs leading to discontinuation from study;
- TEAE of Special Interest;
- Treatment-related TEAE of Special Interest;
- Non-fatal serious TEAE;

An AE is considered an AE of Special Interest if on the AE eCRF the answer to the item "Is this an AE of Special Interest?" is "Yes". For specific criteria used to identify AEs of Special Interest refer to section 8.5.6 of the protocol.

Overall AE listing will include the treatment arm, start and stop dates/times of the AE, treatment dates/times, and treatment emergent status.

A Treatment related AE is defined as an AE for which the investigator classifies the AE as being "Possibly Related" or "Probably Related" to study treatment on Adverse Event eCRF. Missing relationship and severity (intensity) will be imputed per Section 4.2.3.

Additional summary table will be provided for AEs that occurred on or after the study dose through 48 weeks after the study dose administration and after additional OAB medication was taken, or initiation of investigational agent, or surgical intervention.

The following additional listings will be provided:

- Listing of deaths
- Listing of SAEs
- Listing of TEAEs of Special Interest
- Listing of TEAEs leading to study discontinuation

7.3. Laboratory Evaluations

All continuous laboratory parameters in hematology and clinical chemistry will be summarized descriptively by absolute value at each visit by treatment group, together with the corresponding changes from baseline. All parameters will be summarized in SI units. Hemoglobin and Hematocrit will also be summarized in Conventional units.

The number and percentage of subjects with laboratory measurements outside of the central laboratory normal range will also be summarized by treatment group and visit. Shift tables from baseline to maximum post-baseline value, to minimum post-baseline value, last post-

baseline value, and at each post-baseline visit will be provided for hematology and chemistry parameters to display low, normal, high, and missing values by treatment group in a 3-by-3 contingency table. Denominators for percentages will be the number of subjects with non-missing data at the specific assessment and baseline.

A sample for the urinalysis and urine culture will be sent to the central laboratory only if the urine dipstick performed at the site tests positive for the presence of leukocytes, nitrites, or blood cells. Central urinalysis data will only be presented in the listing.

Any data outside the central laboratory normal reference ranges will be explicitly noted on the listings that are produced.

7.4. Vital Signs

Vital sign data including blood pressure, pulse rate, respiration rate, and body temperature will be collected at all study visits except for the telephone follow-up visits. Height will be measured at Screening only.

For all parameters, absolute values and change from baseline will be presented for scheduled visits using descriptive statistics for continuous variables. In addition, the maximum post-baseline, change from baseline to the maximum post-baseline, and change from baseline to the last post-baseline value will be summarized for each of the vital signs.

A by-subject listing, sorted by treatment and subject identifier, will be presented including all vital sign results (scheduled or unscheduled).

7.5. ECG

12-Lead ECG data will be collected at the screening visit and at Week 2, 12, and 24 visits. For all parameters, absolute values and change from baseline will be presented for scheduled visits using descriptive statistics for continuous variables. The evaluation result will be summarized at each visit as well.

A by-subject listing, sorted by treatment and subject identifier, will be presented including all ECG results (scheduled or unscheduled).

7.6. Physical Examination

Physical examination data will be collected at Screening and Week 24. Shift tables (normal, abnormal, not done) of baseline versus the last observation post-baseline [normal, abnormal (same as baseline), abnormal (new or aggravated), not done] may be generated, presenting the assessment for each component of the physical examination separately. Listing of abnormal results will be produced.

7.7. PVR

The volume of urine that remains in the bladder after voiding is an objective measurement that may serve as a proxy for impaired ability to void. Absolute values and change from baseline will be presented for scheduled visits using descriptive statistics for PVR measurements. In addition, the maximum post-baseline, change from baseline to the maximum post-baseline, and change from baseline to the last post-baseline value will be summarized. The maximum and the last post-baseline value will not use the visit windows rules and any non-missing post-baseline values will be used for the derivation. A categorical summary will be based on the following levels:

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

All PVR measurements will be listed.

7.8. Clean Intermittent Catheterization (CIC)

For subjects with CIC initiated, time from study drug injection to the start of CIC (in days) and length of CIC use (in days) will be summarized by treatment arms. If CIC is used more than once, the length will be summed together for summary purpose. No imputation will be done for CIC start and stop dates. All CIC information will be provided in the listing.

7.9. Bladder and Kidney Ultrasound

Bladder and Kidney ultrasound results will not be summarized and will be provided in the listing.

8. COVID-19 CONSIDERATIONS

This study was conducted during the COVID-19 global pandemic. During the time period of the pandemic, it is anticipated that changes in study visit schedules, missed visits, or patient discontinuations may lead to missing information (e.g., for protocol-specified procedures). In accordance with the FDA guidance of conduct of clinical trials of medical produces during COVID-19 public health emergency, it is important to capture specific information in the case report form that explains the basis of the missing data, including the relationship to COVID-19 for missing protocol-specified information (e.g., from missed study visits or study discontinuations due to COVID-19).

The proportion of subjects with COVID-19 impact on visits will be summarized by treatment group overall and by visit. The reasons (e.g. subject acquired COVID-19, Subject unable to travel due to COVID-19, investigative site closure due to COVID-19, etc) will also be summarized. A listing of subjects who had a COVID-19 information collected will be generated which will document the date of contact, update to AE or concomitant medication since the last visit, and whether the bladder diaries were completed.

9. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

Protocol section 9.3 defined analyses population. In the SAP Section 3.1, safety (modified) population was removed.

Protocol section 3.2.1 defined exploratory efficacy endpoints. In the SAP Section 1.1.1 and Section 4.3.2 , 'Nighttime voids' was added as an exploratory efficacy endpoint.

In the SAP Section 7.2 the definition of treatment-emergent adverse event was updated to include the additional OAB medication as the end of the treatment-emergent period in addition to the initiation of the investigational agent and/or surgical intervention.

In Protocol section 9.5.1 PGI-C change from baseline was analyzed using MMRM method. In the SAP section 4.3.3 and 6.2 the analysis method for PGI-C was changed to use the responder analysis with CMH method.

SAP added additional endpoint of proportion of subjects achieving ≥ 50%, ≥ 75% and 100% reduction in average daily UI episodes.

[redacted]

Since no analysis plan is definitive especially for this exploratory study, we may perform additional data driven sensitivity analysis.

10. REFERENCES

[1] B. Schurch, P. Denys, C. M. Kozma, P. R. Reese, T. Slaton, and R. Barron, "Reliability and Validity of the Incontinence Quality of Life Questionnaire in Patients With Neurogenic Urinary Incontinence," *Arch. Phys. Med. Rehabil.*, vol. 88, no. 5, pp. 646–652, May 2007, doi: 10.1016/j.apmr.2007.02.009.
[2] K. S. Coyne, C. L. Thompson, J.-S. Lai, and C. C. Sexton, "An overactive bladder symptom and health-related quality of life short-form: Validation of the OAB-q SF:

Validation of the OAB-q SF," *Neurourol. Urodyn.*, vol. 34, no. 3, pp. 255–263, Mar. 2015, doi: 10.1002/nau.22559.

[3] S. Greenland and J. M. Robins, "Estimation of a Common Effect Parameter from Sparse Follow-Up Data," *Biometrics*, vol. 41, no. 1, p. 55, Mar. 1985, doi: 10.2307/2530643.

11. APPENDIX

11.1. Table of Contents for Data Display Specifications

11.1.1. Output Tables

Table 8: List of Output Tables

Title		Population	Programming Note	Deliverable
Study Population				
14.1.1.1	Subject Enrollment	Screened		EOS
14.1.1.2	Subject Disposition	Randomized		TL, EOS
14.1.1.3	Subject Randomization by Investigator	Randomized		EOS
14.1.2.1	Major Protocol Deviations	Randomized		EOS
14.1.2.2	Reasons for Exclusion from Analysis	Randomized		EOS
14.1.3.1	Demographics and Baseline Characteristics	ITT-E		TL, EOS
14.1.4	Medical History	ITT-E		EOS
14.1.5.1	Prior Medication	ITT-E	ATC Level 2 and 4	EOS
14.1.5.2	Concomitant Medication	ITT-E	ATC Level 2 and 4	EOS
14.1.5.3	Additional OAB Treatment Received Prior to Week 24 (Medication)	ITT-E	ATC Levels 2, 4 and PT	TL, EOS
14.1.5.4	Additional OAB Treatment Received at or After Week 24 (Medication)	ITT-E	ATC Levels 2, 4 and PT	TL, EOS
14.1.5.5	Additional OAB Treatment Received Prior to Week 24 (Procedure)	ITT-E	ATC Levels 2, 4 and PT	EOS

Title		Population	Programming Note	Deliverable
14.1.5.6	Additional OAB Treatment Received at or After Week 24 (Procedure)	ITT-E	ATC Levels 2, 4 and PT	EOS
14.1.6	COVID-19 Impact	ITT-E		EOS
Efficacy Endpoints				EOS
14.2.1.1	Change from Baseline in Average Daily Number of Urge Urinary Incontinence Episodes (MMRM)	ITT-E	Week 12 first, then other visits sequentially	TL, EOS
14.2.1.2	Summary of Average Daily Number of Urge Urinary Incontinence Episodes	ITT-E	By-visit Descriptive Summary	TL, EOS
14.2.1.3	Summary of Average Daily Number of Urge Urinary Incontinence Episodes by Baseline UUI Episodes per Day	ITT-E	Subgroup columns within each treatment arm	EOS
14.2.1.4	Summary of Average Daily Number of Urge Urinary Incontinence Episodes by Presence or absence of DO	ITT-E	Subgroup columns within each treatment arm	EOS
14.2.1.5	Summary of Average Daily Number of Urge Urinary Incontinence Episodes by Previous Use of onabotulinumtoxinA	ITT-E	Subgroup columns within each treatment arm	EOS
14.2.1.6	Change from Baseline in Average Daily Number of Urge Urinary Incontinence Episodes at Week 12	ITT-E		EOS
14.2.1.7	Change from Baseline in Average Daily Number of Urge Urinary Incontinence Episodes (MMRM) - Sensitivity Analysis	ITT-ES	Week 12 first, then other visits sequentially	EOS
14.2.2.1	Change from Baseline in Average Daily Number of Micturitions (MMRM)	ITT-E	Week 12 first, then other visits sequentially	TL, EOS
14.2.2.2	Summary of Average Daily Number of Micturitions	ITT-E	By-visit Descriptive Summary	TL, EOS
14.2.2.3	Summary of Average Daily Number of Micturitions by Baseline UUI Episodes per Day	ITT-E	Subgroup columns within each treatment arm	EOS
14.2.2.4	Summary of Average Daily Number of Micturitions by Presence or absence of DO	ITT-E	Subgroup columns within each treatment arm	EOS

Title		Population	Programming Note	Deliverable
14.2.2.5	Summary of Average Daily Number of Micturitions by Previous Use of onabotulinumtoxinA	ITT-E	Subgroup columns within each treatment arm	EOS
14.2.2.6	Change from Baseline in Average Daily Number of Micturitions at Week 12	ITT-E		EOS
14.2.2.7	Change from Baseline in Average Daily Number of Micturitions (MMRM) - Sensitivity Analysis	ITT-ES	Week 12 first, then other visits sequentially	EOS
14.2.3.1	Change from Baseline in Average Daily Number of Urinary Incontinence Episodes (MMRM)	ITT-E	Week 12 first, then other visits sequentially	TL, EOS
14.2.3.2	Summary of Average Daily Number of Urinary Incontinence Episodes	ITT-E	By-visit Descriptive Summary	TL, EOS
14.2.3.3	Summary of Average Daily Number of Urinary Incontinence Episodes by Baseline UUI Episodes per Day	ITT-E	Subgroup columns within each treatment arm	EOS
14.2.3.4	Summary of Average Daily Number of Urinary Incontinence Episodes by Presence or absence of DO	ITT-E	Subgroup columns within each treatment arm	EOS
14.2.3.5	Summary of Average Daily Number of Urinary Incontinence Episodes by Previous Use of onabotulinumtoxinA	ITT-E	Subgroup columns within each treatment arm	EOS
14.2.4.1	Change from Baseline in Average Daily Number of Urgency Episodes (MMRM)	ITT-E	Week 12 first, then other visits sequentially	TL, EOS
14.2.4.2	Summary of Average Daily Number of Urgency Episodes	ITT-E	By-visit Descriptive Summary	TL, EOS
14.2.4.3	Summary of Average Daily Number of Urgency Episodes by Baseline UUI Episodes per Day	ITT-E	Subgroup columns within each treatment arm	EOS
14.2.4.4	Summary of Average Daily Number of Urgency Episodes by Presence or absence of DO	ITT-E	Subgroup columns within each treatment arm	EOS
14.2.4.5	Summary of Average Daily Number of Urgency Episodes by Previous Use of onabotulinumtoxinA	ITT-E	Subgroup columns within each treatment arm	EOS
14.2.5.1	Change from Baseline in Average Volume Voided per Micturition (MMRM)	ITT-E	Week 12 first, then other visits sequentially	TL, EOS

Title		Population	Programming Note	Deliverable
14.2.5.2	Summary of Average Volume Voided per Micturition	ITT-E	By-visit Descriptive Summary	TL, EOS
14.2.6.1	Proportion of Subjects Achieving >= 50% Reduction in Number of Average Daily Urge Urinary Incontinence Episodes from Baseline	ITT-E	Week 12 first, then other visits sequentially	EOS
14.2.6.2	Proportion of Subjects Achieving >= 75% Reduction in Urge Urinary Incontinence Episodes from Baseline	ITT-E	Week 12 first, then other visits sequentially	EOS
14.2.6.3	Proportion of Subjects achieving 100% Reduction in Urge Urinary Incontinence Episodes from Baseline	ITT-E	Week 12 first, then other visits sequentially	TL, EOS
14.2.7.1	Change from Baseline I-QOL Domains (MMRM)	ITT-E	Week 12 first, then Week 6	TL, EOS
14.2.7.2	Summary of I-QOL Scores	ITT-E	By-visit Descriptive Summary	TL, EOS
14.2.7.3	Proportion of Subjects Achieving the Minimally Important Difference in I-QOL Total Summary Score	ITT-E	Week 12 first, then Week 6	EOS
14.2.8.1	Change from Baseline in OAB-q Scores (MMRM)	ITT-E	Week 12 first, then Week 6	TL, EOS
14.2.8.2	Summary of OAB-q Scores	ITT-E	By-visit Descriptive Summary	TL, EOS
14.2.9.1	Change from Baseline on Patient Global Impression Change Score at Week 12	ITT-E	Week 12 only	TL, EOS
14.2.9.2	Summary of Patient Global Impression	ITT-E	By-visit Descriptive summary and change from baseline of numeric score	EOS
14.2.10	Summary of Urodynamic Parameters	ITT-E	Baseline and Week 12 only	EOS
14.2.11	Summary of hSlo cDNA Concentrations	ITT-E		TL, EOS
14.2.12.1	Change from Baseline in Average Daily Number of Nighttime Voids (MMRM)	ITT-E	Week 12 first, then other visits sequentially	EOS

Title		Population	Programming Note	Deliverable
14.2.12.2	Summary of Average Daily Number of Nighttime Voids	ITT-E	By-visit Descriptive Summary	EOS
14.2.13.1	Proportion of Subjects Achieving >= 50% Reduction in Number of Average Daily Urinary Incontinence Episodes from Baseline	ITT-E	Week 12 first, then other visits sequentially	EOS
14.2.13.2	Proportion of Subjects Achieving >= 75% Reduction in Number of Average Daily Urinary Incontinence Episodes from Baseline	ITT-E	Week 12 first, then other visits sequentially	EOS
14.2.13.3	Proportion of Subjects Achieving 100% Reduction in Number of Average Daily Urinary Incontinence Episodes from Baseline	ITT-E	Week 12 first, then other visits sequentially	EOS
Safety Endpoints				
Adverse Events				
14.3.1.1	Overall Treatment-Emergent Adverse Events	Safety		TL, EOS
14.3.1.2.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety	Sort by SOC and PT in descending frequency of URO-902 arms combined.	TL, EOS
14.3.1.2.2	Treatment-Emergent Adverse Events Occurring between Weeks 1 and 24 by System Organ Class and Preferred Term	Safety	Sort by SOC and PT in descending frequency of URO-902 arms combined.	EOS
14.3.1.2.3	Treatment-Emergent Adverse Events Occurring between Weeks 24 and 48 by System Organ Class and Preferred Term	Safety	Sort by SOC and PT in descending frequency of URO-902 arms combined.	EOS
14.3.1.3.1	Treatment-Emergent Adverse Events by Preferred Term	Safety	Sort by PT in descending frequency of URO-902 arms combined. Same for all subsequent tables	TL, EOS
14.3.1.3.2	Treatment-Related Treatment-Emergent Adverse Events by Preferred Term	Safety		EOS

Title		Population	Programming Note	Deliverable
14.3.1.4	Treatment-Emergent Adverse Events by Preferred Term and Maximum Intensity	Safety		EOS
14.3.1.5	Treatment-Emergent Adverse Events with Grade ≥ 3 by Preferred Term	Safety		EOS
14.3.1.6	Treatment-Related Treatment-Emergent Adverse Events with Grade ≥ 3 by Preferred Term	Safety		EOS
14.3.1.7	Serious Treatment-Emergent Adverse Events by Preferred Term	Safety		TL, EOS
14.3.1.8	Treatment-Related Serious Treatment-Emergent Adverse Events by Preferred Term	Safety		EOS
14.3.1.9	Fatal Treatment-Emergent Adverse Events by Preferred Term	Safety		EOS
14.3.1.10	Treatment-Emergent Adverse Events Leading to Study Discontinuation by Preferred Term	Safety		TL, EOS
14.3.1.11	Treatment-Emergent Adverse Events of Special Interest by Preferred Term	Safety		EOS
14.3.1.12	Treatment-Related Treatment-Emergent Adverse Events of Special Interest by Preferred Term	Safety		EOS
14.3.1.13	Non-Fatal Serious Treatment-Emergent Adverse Events by Preferred Term	Safety		EOS
14.3.1.14	Adverse Events Occurred After Study Dose Through Week 48 and After Initiation of Another OAB Medication, Investigational Agent, or Surgical Intervention	Safety	Same Layout as the Overall AE Summary Table 14.3.1.1	EOS
14.3.2.6	List of Deaths	Safety		EOS
14.3.2.7	Listing of Serious Adverse Events	Safety		EOS
14.3.2.8	Listing of Treatment-Emergent Adverse Events Leading to Study Discontinuation	Safety		EOS

Title		Population	Programming Note	Deliverable
14.3.2.9	Listing of Treatment-Emergent Adverse Events of Special Interest	Safety		EOS
Laboratory data				
14.3.3.1	Hematology Laboratory Parameters	Safety	Include observed and CFB	EOS
14.3.3.2	Abnormal Classification of Hematology Laboratory Parameters	Safety		EOS
14.3.3.3	Shift Table of L/N/H Classification for Hematology Laboratory Parameters from Baseline	Safety	Include max/min post-dose, by visit, last-post dose	EOS
14.3.3.4	Clinical Chemistry Laboratory Parameters	Safety	Include observed and CFB	EOS
14.3.3.5	Abnormal Classification of Clinical Chemistry Laboratory Parameters	Safety		EOS
14.3.3.6	Shift Table of L/N/H Classification for Clinical Chemistry Laboratory Parameters from Baseline	Safety	Include max/min post-dose, by visit, last-post dose	EOS
Other Safety				
14.3.4	Vital Sign Parameters	Safety	Include all observed and CFB	EOS
14.3.5	Electrocardiograms Parameters	Safety	Include all observed and CFB	EOS
14.3.6	Physical Examination Shift from Baseline	Safety		EOS
14.3.7	Post-void Residual Urine Volume	Safety	Include all observed and CFB	TL, EOS
14.3.8	Clean Intermittent Catheterization	Safety		EOS

11.1.2. Output Figures

Table 9: List of Output Figures

Title		Population	Programming Note	Deliverable
Efficacy Endpoints				
14.2.1.1	Line Plots of LSMEAN (SE) of Change from Baseline in Average Daily Number of UUI Episodes from MMRM	ITT-E	Include all individual weeks	TL, EOS
14.2.1.2	Line Plots of LSMEAN (SE) of Change from Baseline in Average Daily Number of Micturitions from MMRM	ITT-E	Include all individual weeks.	TL, EOS
14.2.1.3	Line Plots of LSMEAN (SE) of Change from Baseline in Average Daily Number of UI Episodes from MMRM	ITT-E	Include all individual weeks.	EOS
14.2.1.4	Line Plots of LSMEAN (SE) of Change from Baseline in Average Daily Number of Urgency Episodes from MMRM	ITT-E	Include all individual weeks.	EOS
14.2.1.5	Line Plots of LSMEAN (SE) of Change from Baseline in Average Volume Voided per Micturition from MMRM	ITT-E	Include all individual weeks.	EOS
14.2.1.6	Line Plots of LSMEAN (SE) of Change from Baseline in Average Daily Number of Nighttime Voids from MMRM	ITT-E	Include all individual weeks.	EOS
14.2.1.7	Line Plots of LSMEAN (SE) of Change from Baseline in Total Summary Score from I-QOL	ITT-E		EOS
14.2.1.8	Kaplan Meier Plot of Time to Study Discontinuation	Safety		EOS

11.1.3. Output Listings

Table 8: List of Output Listings

Title		Population	Programming Note	Deliverable
Disposition and Demographics				
16.2.1.1	Listing of Subject Disposition for Screen Failures	Screened		EOS
16.2.1.2	Listing of Subject Disposition	Randomized		EOS
16.2.1.3	Listing of Subjects who did not Satisfy Inclusion/Exclusion Criteria	Screened		EOS
16.2.1.4	Listing of Subject Randomization Details	Randomized		EOS
16.2.1.5	Listing of Major Protocol Deviations	Randomized		EOS
16.2.1.6	Listing of Subject Demographic and Baseline Characteristics	ITT-E		EOS
16.2.1.7	Listing of Medical History	ITT-E		EOS
16.2.1.8	Listing of Prior and Concomitant Medications	ITT-E		EOS
16.2.1.9	Listing of Additional OAB Medications	ITT-E		EOS
16.2.1.10	Listing of Additional OAB Procedures	ITT-E		EOS
16.2.1.11	COVID-19 Impact	ITT-E		EOS
16.2.1.12	Listing of Analysis Populations	Randomized		EOS
Efficacy				EOS
16.2.2.1	Listing of Bladder Diary	ITT-E		EOS
16.2.2.2	Listing of I-QOL Scores	ITT-E		EOS
16.2.2.3	Listing of OAB-q Scores	ITT-E		EOS
16.2.2.4	Listing of Patient Global Impression Scale Scores	ITT-E		EOS
16.2.2.5	Listing of Urodynamic Parameters	ITT-E		EOS
16.2.2.6	Listing of hSlo cDNA Concentrations	ITT-E		EOS
Safety				

Title		Population	Programming Note	Deliverable
16.2.3.1	Listing of Treatment Exposure	Safety		EOS
16.2.3.2	Listing of Adverse Events	Safety		EOS
16.2.3.3	Listing of Hematology Laboratory Results	Safety		EOS
16.2.3.4	Listing of Clinical Chemistry Laboratory Results	Safety		EOS
16.2.3.5	Listing of Urinalysis Laboratory Results	Safety		EOS
16.2.3.6	Listing of Vital Sign Results	Safety		EOS
16.2.3.7	Listing of ECG Results	Safety		EOS
16.2.3.8	Listing of Physical Examination	Safety		EOS
16.2.3.9	Listing of Post-void Residual Urine Volume	Safety		EOS
16.2.3.10	Listing of Clean Intermittent Catheterization	Safety		EOS
16.2.3.11	Listing of Bladder and Kidney Ultrasound	Safety		EOS