# 1. Title Page

**STATISTICAL ANALYSIS PLAN**

**A Two-part, Multicenter, Dose-titration Study Evaluating the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Oxybutynin Chloride 10% Gel for the Treatment of Detrusor Overactivity Associated With a Neurological Condition in Pediatric Patients**

**Final 2.0: 2022-03-28**

| | |
|---|---|
| Protocol Number: | OG09002 Protocol Amendment 3 |
| Development Phase: | 4 |
| Product Name: | Oxybutynin Chloride 10% Gel |
| Study Statistician: | [redacted] PhD (Version 1.0)<br>[redacted] PhD (Version 2.0)<br>[redacted] PhD (Version 2.0) |
| Sponsor: | Allergan Sales, LLC<br>2525 Dupont Drive<br>Irvine, CA 92612 |

## 2. Table of Contents

## 2.1 List of Tables

# 3. List of Abbreviations and Definition of Terms

**Table 3-1 Abbreviations and Definitions of Terms**

| Abbreviation/Term | Definition |
|---|---|
| AE | adverse event |
| ANCOVA | analysis of covariance |
| ATC | Anatomical Therapeutic Chemical |
| CFB | change from baseline |
| CIC | clean intermittent catheterization |
| DEO | N-desethyloxybutynin |
| ECG | electrocardiogram, electrocardiographic |
| eCRF | electronic case report form |
| GCP | Good Clinical Practice |
| ICH | International Conference on Harmonisation |
| ITT | intent-to-treat |
| LOCF | last observation carried forward |
| LS | least squares |
| MedDRA | Medication Dictionary for Regulatory Activities |
| OC | observed cases |
| PCS | potentially clinically significant |
| PK | pharmacokinetic |
| PP | per-protocol |
| PT | preferred term |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SEM | standard error of mean |
| SI | Le Système International d'Unités (International System of Units) |
| SOC | system organ class |
| TEAE | treatment-emergent adverse event |
| WHO | World Health Organization |

# 4. Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the efficacy and safety data outlined and/or specified in the final protocol of Study OG09002. Specifications of tables, figures, and data listings are contained in a separate document. Statistical analysis plan for pharmacokinetics data will be addressed separately.

This document is organized into 3 main sections:

1. Study overview including study design and objectives
2. Statistical Methodology and Study Endpoints
3. Data Handling and Analysis Conventions

## 4.1 Study Design Summary

This study was initiated as a double-blind, placebo-controlled study with an open-label extension and was amended via protocol amendment (Protocol Amendment 3) to enroll participants under only open-label treatment. Therefore, analyses are described with respect to prior to protocol amendment 3 ("pre-amendment 3") and with protocol amendment 3 ("post-amendment 3").

**Prior to Amendment 3**, participants aged 6 years to < 17 years who had a diagnosis of detrusor overactivity associated with a neurological condition and were using clean intermittent catheterization (CIC) to control bladder function were randomly assigned 1:1 to receive double-blind oxybutynin chloride gel or placebo gel for 6 weeks. Enrollment was stratified based on sex, age, and weight. Stratification was done within the following groups: male and female; 6 to < 12 years-of-age and 12 to < 17 years-of-age; and by weight category: ≤ 25.0 kg and > 25.0 kg for the 6 to < 12 years-of-age group and ≤ 50.0 kg and > 50.0 kg for the 12 to < 17 years-of age group. Enrollment into the 6-week treatment period was to be followed by an open-label, 8-week period to generate safety data. All participants began treatment with 0.75 g of gel/day for 2 weeks. Participants then returned to the clinic at Week 2 for a potential dose titration and at this time their dose could have been adjusted up to 1 g/day, down to 0.5 g/day, or remained the same at 0.75 g/day. The determination of dose was based on the investigator's clinical judgment and assessment of the patient's bladder symptoms and treatment side effects. Dose titration was permitted only once during the entire 6-week double-blind, placebo-controlled period. Participants continued blinded treatment for 4 additional weeks until the end of the double-blind treatment period.

**Post-Amendment 3**, the study became a multicenter, open-label, dose-titration study in pediatric participants, ages 3 years to < 17 years, with detrusor overactivity associated with a neurological condition. A minimum of 25 participants are to be enrolled. Efforts will be made to enroll a greater number of participants from the ages of 3 years to < 6 years. Participants must be suitable

candidates for anticholinergic therapy and must be using CIC for bladder control. The study will include a screening period from Day -13 to Day -5 and a 14-week open-label treatment period. The expected duration of the study for each patient will be up to 16 weeks (which includes 2 weeks of screening and 14 weeks of treatment). There are six clinic visits (Visit A – Visit F). No changes were made in the starting dose, compared to the Pre-Amendment 3 study design, in that all participants will begin treatment with 0.75 g of gel/day for 2 weeks. Participants will then return to the clinic for a potential dose titration and at this time their dose may be adjusted up to 1 g/day, down to 0.5 g/day, or remain the same at 0.75 g/day, depending on individual response and tolerability. The determination of dose will be based on the investigator's clinical judgment and assessment of the patient's bladder symptoms and treatment side effects. Dose titration will be permitted only once during the entire 14-week treatment period (at Visit C, Week 2). Participants will continue the adjusted dose for 12 additional weeks until the end of the open-label treatment period.

Safety will be evaluated by monitoring adverse events, physical examinations, vital signs, clinical laboratory evaluations, skin erythema at the application site, and a vision symptom questionnaire.

## 4.2 Study Objectives and Endpoints

Each study objective is presented with endpoint(s) below:

| Objectives | Endpoints |
|---|---|
| **Primary**<br>• **Pre-Amendment 3**: To evaluate the efficacy of daily treatment with oxybutynin chloride gel compared to placebo in pediatric participants during the first 6 weeks (i.e., the double-blind treatment period) of a 14-week treatment period<br>• **Post-Amendment 3**: To evaluate the efficacy of daily treatment with oxybutynin chloride gel in pediatric participants during the first 6-weeks of a 14-week open-label treatment period | **Primary Efficacy Endpoints**<br>• Change from baseline to Week 6 of treatment or to the last observation carried forward (LOCF) in the percentage of catheterizations without a leaking accident as recorded in the 2-day urinary diary<br><br>**Secondary Efficacy Endpoints**<br>• Change from baseline to Week 6 of treatment in the following (calculated from the 2-day urinary diary data):<br>o Average volume of urine collected per catheterization (for Pre-Amendment 3 population only)<br>o Average volume of urine collected at first (morning awakening) catheterization<br>o Average number of catheterizations per day |

| Objectives | Endpoints |
|---|---|
| **Secondary**<br>• To evaluate the pharmacokinetics, pharmacodynamics, safety, and skin, tolerability of oxybutynin chloride gel in pediatric participants | **Pharmacokinetic Endpoints:**<br>• Plasma concentration for Oxybutynin (OXY) and N-desethyloxybutynin (DEO) plasma concentrations for the R- isomer, S-isomer, and R+S<br>• The ratio of DEO to OXY<br>  <br>**Safety Assessments**:<br>• Adverse events (AE), clinical laboratory values, vital signs, and physical examinations<br>• Skin Tolerability of Oxybutynin Assessment: Skin assessments for Erythema<br>**Other Assessments**:<br>• Anticholinergic Symptoms Questionnaire<br>• Vision Symptom Questionnaire |

## 4.3 Schedule of Events

**Post-Amendment 3**

| Evaluation: | Screening Period | Open-Label Treatment Period | | | | |
|---|---|---|---|---|---|---|
| | Visit A[1] | Visit B | Visit C | Visit D | Visit E | Visit F/ ET |
| | -13 to -5 Days | Week 0 | Week 2 | Week 6 | Week 10 | Week 14 |
| Informed Consent | X | | | | | |
| I/E Criteria | X | X | | | | |
| Medical History | X | X | | | | |
| Vision Assessment in Children < 8 years | X[2] | | | | | |
| Concomitant Medication | X | X | X | X | X | X |
| Demographic Information | X | | | | | |
| Physical Examination | X | | | | | X |
| Height and Weight | X | | | | | |
| Vital Signs | X | X | X | X | X | X |
| 12-Lead ECG | X | | | | | |
| Serum Chemistries | X | | | | | X |
| Hematology | X | | | | | X |
| Urinalysis | X | X[3] | | | | X |
| Urine Culture | X | | | | | |
| Urine pregnancy test[4] | X | | | X | | X |
| Urodynamics | | X | | X | | |
| Dispense 2-day Urinary Diary | X | | X | | | |
| Collect 2-day Urinary Diary | | X | | X | | |
| Local Erythema Assessment [5] | | | X | X | X | X |
| Adverse Event Assessment | | | X | X | X | X |
| Anticholinergic Questionnaire | | X | X | X | X | X |
| Vision Symptom Questionnaire | | X | X | X | X | X |
| Collect PK Sample & Record Date/Time | | | X | X | | X |
| Dose Titration (if necessary) | | | X | | | |
| Study Drug Dispensing | | X[6] | X[6] | X | X | |
| Study Treatment Compliance | | | X | X | X | X |

1 All participants taking anticholinergic medications will be asked to discontinue treatment and complete a 3-day washout period (11-day washout period if the patient was previously taking solifenacin).
2 Vision Assessment is required prior to or at the Baseline Visit for participants < 8 years of age, at the time of screening who have not received a vision screening assessment within the last 12 months prior to screening.
3 A urine sample for on-site urinalysis to determine presence of bacterial infection will be collected.
4 Urine pregnancy test will only be performed for females of childbearing potential.
5 Assessment for local erythema at application site.
6 Instruct patient/caregiver on study treatment application**.**

**Pre-Amendment 3**

The schedule of events for Pre-Amendment 3 is found in Appendix 1 of this document.

# 5. Statistical Methodology and Study Endpoints

## 5.1 Statistical Methods Planned in the Protocol and Determination of Sample Size

This SAP will be approved prior to database lock. The SAP expands the statistical section of the protocol and contains a detailed description of methods to analyze data collected in the study. The text portion of the SAP will be included in the CSR report as Appendix 16.1.9.

### 5.1.1 Statistical and Analytical Plans

Statistical analyses will be conducted using SAS Version 9.3 or newer.

#### 5.1.1.1 Common Conventions

##### 5.1.1.1.1 Analysis Populations

The analysis populations will consist of participants as defined below, where analysis populations are formed relative to the protocol under which a participant was enrolled. Participants enrolled prior to protocol amendment 3 are referred to as “pre-amendment 3,” and participants enrolled under protocol amendment 3 or later are referred to as “post-amendment 3.” For example, the pre-amendment 3 safety population consists of all treated participants who received blinded study treatment and may have also received open-label active treatment. The post-amendment 3 safety population consists of all treated participants who received open-label active treatment. Details are below with categorizations based on double-blind or open-label treatment.

**Table 5-1 Analysis Populations**

| Population | Definition | Study Treatment |
|---|---|---|
| Post-Amendment 3 open-label **Safety** | All participants who receive at least 1 dose of study treatment in the open-label period who are enrolled under Amendment 3 or later | Actual received[1] |
| Pre-Amendment 3 double-blind **Safety** | All participants who receive at least 1 dose of study treatment in the double-blind period, which is only applicable to participants who enrolled prior to Amendment 3 | Actual received[1] |
| Pre-Amendment 3 open-label **Safety** | All participants who receive at least 1 dose of study treatment in the open-label period before Amendment 3 | Actual received[1] |
| Combined open-label **Safety** (Pre- and Post-Amendment 3) | All participants who receive at least 1 dose of study treatment in the open-label period before or after Amendment 3 | Actual received[1] |
| Post-Amendment 3 Intent-to-Treat (**ITT**)[2] | All participants who receive at least 1 dose of study treatment and have at least one post-baseline value for the primary efficacy variable in the Post-Amendment 3 open-label period | Actual received[1] |
| Pre-Amendment 3 (Intent-to-Treat) **ITT**[2] | All randomized participants who have at least one post-baseline value for the primary efficacy variable in the Pre-Amendment 3 double-blind period | Randomized assignment |
| Combined Intent-to-Treat (**ITT**[2]) (Pre- and Post-Amendment 3) | All participants who receive at least 1 dose of study treatment and have at least one post-baseline value for the primary efficacy variable in the Post-Amendment 3 open-label period and all randomized participants who have at least one post-baseline value for the primary efficacy variable in the Pre-Amendment 3 double-blind period | Actual received or Randomized assignment[3] |
| Post-Amendment 3 Per-Protocol (**PP**) | All participants in the Post-Amendment 3 ITT population who complete the Post-Amendment 3 open-label treatment period of the study and who are without significant protocol violations | Actual received[1] |
| Pre-Amendment 3 Per-Protocol (**PP**) | All participants in the Pre-Amendment 3 ITT population who complete the double-blind treatment period of the study and who are without significant protocol violations | Randomized assignment |

1 Participants will be summarized according to the study treatment received for majority of the treatment period.

2 The primary efficacy variable in the description of each ITT population definition is the change from baseline (CFB) to Week 6 of treatment or the last observation carried forward (LOCF) in the percentage of catheterizations without a leaking accident as recorded in the 2-day urinary diary.

3 Actual treatment received for Post-Amendment 3 open-label data and Randomized treatment for Pre-Amendment 3 double-blind treatment period data.

#### 5.1.1.1.2 Study Treatments

The following treatment groups are defined for this study:

- Oxybutynin chloride gel in the Post-Amendment 3 open-label period (titrated dose levels of 0.5, 0.75, and 1.0 g of oxybutynin chloride gel per day)
- Placebo in the Pre-Amendment 3 double-blind period
- Oxybutynin chloride gel in the Pre-Amendment 3 double-blind period (titrated dose levels of 0.5, 0.75, and 1.0 g of oxybutynin chloride gel per day)
- Oxybutynin chloride gel in the Pre-Amendment 3 open-label period (titrated dose levels of 0.5, 0.75, and 1.0 g of oxybutynin chloride gel per day)

#### 5.1.1.1.3 Statistical Methodology

The methodologies defined below apply as specified to individual endpoints defined in this SAP. When indicated, two-sided 95% confidence intervals and two-sided p-values will be presented. Individual endpoint analyses may specify exceptions (additions or deletions) to these general definitions.

**Table 5-2 Statistical Methodology**

| Methodology | Description |
|---|---|
| Categorical counts | • Number of participants in individual categories<br>  ○ Participants with ≥ 1 qualifying event counted once per individual category |
| Categorical descriptives | • Number and percentage of participants in individual categories<br>  ○ Participants with ≥ 1 qualifying event counted once per individual category<br>  ○ N1 = participants with a non-missing baseline value |
| Shift analysis | • Number and percentage of participants in individual baseline and postbaseline categories<br>• Percentage denominator = number of participants in individual baseline categories<br>• N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit<br>• Shifts include: Normal → Low, Normal → High, High → Low, High → Normal, Low → High, Low → Normal for continuous variables and Normal → Abnormal for categorical variables |
| Continuous descriptives | • N1, mean, standard deviation (SD), median, minimum, maximum, 25$^{th}$ percentile, 75$^{th}$ percentile, standard error of mean (SEM) for a visit in an analysis group<br>• N1 = participants with non-missing value for a visit in an analysis group |
| CFB descriptives | • Continuous descriptives for baseline, postbaseline, and change from baseline (CFB) values for an analysis group<br>• N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit for an analysis group |
| CFB one-sample t-test | • Estimates derived from one-sample t-test at an analysis visit (observed case [OC] or LOCF, e.g., Week 6 LOCF) for an analysis group<br>  ○ mean and 95% confidence interval (CI)<br>  ○ P-value<br>• N1=participants with non-missing values at both baseline and the specified postbaseline analysis visit (in the Post-Amendment 3 ITT and PP populations and in the Pre-Amendment 3 and Post-Amendment 3 ITT and PP populations, including for each sex, within an age group, or within an weight category within an age group) |
| CFB ANCOVA | • Continuous descriptives and standard error (SE) for baseline, postbaseline, and CFB values at an analysis visit (e.g., Week 6 LOCF)<br>• Estimates derived from a model for CFB value controlling for factors (treatment group) and covariates (baseline value)<br>  ○ Least squares (LS) means and standard errors<br>  ○ LS mean differences, and 95% confidence intervals for oxybutynin chloride gel vs Placebo<br>  ○ P-values from contrast t-test comparing oxybutynin chloride gel vs Placebo<br>• N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit |
| Exact (Clopper-Pearson) 95% CI | • Exact 95% CI for a single proportion |

| Methodology | Description |
|---|---|
| Exact unconditional 95% CI using the score statistic | • Exact 95% CI for difference between two proportions |
| Cochran-Mantel-Haenszel (CMH) | • P-value from CMH test controlling for baseline covariates |
| Kolmogorov-Smirnov test | • P-value from exact Kolmogorov-Smirnov test to examine whether two distributions are the same |

CFB = change from baseline; ANCOVA = analysis of covariance.

Raw and derived data listings will be provided, and will be fully defined in the table, figure, and data listing specification document.

#### 5.1.1.1.4 Missing Data

General missing data handling conventions for methodologies in Section 5.1.1.1.3 are summarized as follows:

**Table 5-3 Missing Data Handling by Endpoint Type**

| Parameter type | Timing | Missing Data Handling |
|---|---|---|
| CFB ANCOVA | Treatment Period | • If missing a covariate:<br>  ○ Participant excluded<br>• If missing derived value at the specified post-baseline analysis visit:<br>  ○ Available cases (i.e., observed case [OC] analysis)<br>  ▪ Participant excluded<br>  ○ Last observation carried forward (LOCF)<br>  ▪ Participant included using LOCF-imputed value (last non-missing post-baseline value before the missing value is carried forward to impute the missing value). Baseline value will not be carried forward. |

### 5.1.1.2 Demographics

#### 5.1.1.2.1 Analysis Populations

The distribution of participants within the analysis populations will be summarized as follows:

**Table 5-4 Analysis Population Summaries**

| Population | Description | Methodology |
|---|---|---|
| Combined open-label safety | Distribution by titrated dose level and overall | Categorical counts |
| Combined ITT | Distribution by study part and treatment group, oxybutynin chloride gel dose level and all gel dose levels as applicable | Categorical counts |

#### 5.1.1.2.2 Participant Disposition

Participant disposition encompasses the distribution of participants who enter, complete, and discontinue, along with eCRF-reported discontinuation reasons. Participant disposition will be summarized as follows:

**Table 5-5 Participant Disposition Summaries**

| Parameter | Description | Timing | Methodology |
|---|---|---|---|
| Completion and discontinuation | Summary completion and discontinuation status, including summary of reasons for discontinuation | — | Categorical descriptive |
| ITT population summary | Distribution in the combined ITT population in total and by treatment group; and by study part in total and by treatment group | — | Categorical descriptives |

#### 5.1.1.2.3 Protocol Deviations

Protocol deviations will be defined in a separate document, including importance classification. Protocol deviations will be summarized as follows:

**Table 5-6 Protocol Deviation Summary**

| Parameter | Description | Timing | Methodology |
|---|---|---|---|
| Important protocol deviations | Distribution in the combined ITT population in total and by treatment group; and by study part in total and by treatment group | — | Categorical descriptives |

#### 5.1.1.2.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized as follows:

- Combined ITT population: double-blind period by treatment group and overall and open-label periods by oxybutynin chloride gel dose level and overall
- Combined open-label safety population: by oxybutynin chloride gel dose level and overall
- Post-Amendment 3 open-label safety population: by oxybutynin chloride gel dose level and overall

The following demographic and baseline characteristics will be summarized as described below:

**Table 5-7 Demographic Summaries**

| Parameter | Description | Timing | Methodology |
|---|---|---|---|
| Age | Age (years) relative to informed consent date | Informed consent | Continuous descriptives |
| Age group | • 3 to < 6 years<br>• 6 to < 12 years<br>• 12 to <17 years | Informed consent | Categorical descriptives |
| Sex, race, and ethnicity | • eCRF categories<br>• Race group<br>  ○ White<br>  ○ Non-white | Screening Period | Categorical descriptives |
| Baseline characteristics | • Height (m)<br>• Weight (kg)<br>• Body mass index (BMI) Weight (kg) / height $(m)^2$ | Latest assessment in Screening Period | Continuous descriptives |
| Baseline characteristics | • Age and Weight Category<br>  ○ <=18 kg and 3 to < 6 years<br>  ○ >18 kg and 3 to < 6 years<br>  ○ <=25 kg and 6 to < 12 years<br>  ○ >25 kg and 6 to < 12 years<br>  ○ <=50 kg and 12 to <17 years<br>  ○ >50 kg and 12 to <17 years | Latest assessment in Screening Period | Categorical descriptives |

### 5.1.1.2.5 Medical History

The results of urinary and bowel movement history will be presented for each analysis population as follows:

- Combined open-label safety population: by oxybutynin chloride gel dose level and overall
- Post-Amendment 3 open-label safety population: by oxybutynin chloride gel dose level and overall
- Pre-Amendment 3 double-blind safety population: by treatment group and overall

Other medical history will be presented in a listing.

Urinary and bowel movement history reported as occurring before the Screening Visit will be summarized by treatment group or dose level for the safety populations as follows:

**Table 5-8 Medical History Summary**

| Parameter | Description | Timing | Methodology |
|---|---|---|---|
| Urinary and Bowel Movement history | Urinary and Bowel Movement history was present before the Screening Visit | Screening Period | Categorical descriptives |

#### 5.1.1.2.6 Prior and Concomitant Medications

Prior medication and concomitant medication use will be summarized separately. The results of prior and concomitant medications will be presented for safety populations as follows:

- Combined open-label safety population: by oxybutynin chloride gel dose level and overall
- Post-Amendment 3 open-label safety population: by oxybutynin chloride gel dose level and overall
- Pre-Amendment 3 double-blind safety population: by treatment group and overall

Medications will be coded using the World Health Organization (WHO) Drug Dictionary, Version WHODRUG DDE + HD 3Q2016 or newer. Unique participants who reported medications will be summarized by Anatomical Therapeutic Chemical (ATC) 4 class and PT in total and for each group or groups defined above for the respective safety population as follows:

**Table 5-9 Medication Summaries**

| Parameter | Description | Timing | Methodology |
|---|---|---|---|
| Prior medications | Medications taken ≥ 1 time before the study treatment start date, regardless of medication end date | Screening Period | Categorical descriptives |
| Concomitant medications | Medications taken ≥ 1 time on or after the study treatment start date, regardless of medication start date | Treatment Period | Categorical descriptives |

ATC4 classes will be sorted alphabetically; PTs will be sorted in descending frequency in the highest dose group.

### 5.1.1.3 Efficacy and Pharmacodynamic Analyses

Efficacy analyses will be based on each ITT and PP Population. Pharmacodynamic analyses will be based on the ITT Population.

The following efficacy assessments and terms are defined:

**Table 5-10 Efficacy and Pharmacodynamic Assessments**

| Assessment/Term | Description |
|---|---|
| Urinary diaries | The following parameters are evaluated:<br>• Number of catheterizations per day<br>• Volume of urine collected at each (after morning awakening) catheterization<br>• Leakage incidents between catheterizations |
| Urodynamic Assessment | The following parameters are evaluated:<br>• Maximal bladder capacity<br>• Detrusor pressures at maximum bladder capacity<br>• Maximum amplitude of involuntary detrusor contractions<br>• Volume at first involuntary detrusor contraction<br>• Presence (versus total absence) of involuntary detrusor contractions at > 15 cm $H_2O$ |

| Assessment/Term | Description |
|---|---|

Baseline assessments for applicable efficacy and pharmacodynamic endpoints defined as follows:

**Table 5-11 Efficacy and Pharmacodynamic Endpoint Baseline Definitions**

| Endpoint | Description | Timing |
|---|---|---|
| Parameters in Urinary diaries and Urodynamic Assessment | The available value at the baseline visit | Visit 1/Visit 2[1] for Pre-Amendment 3,<br>Visit A/Visit B for Post-Amendment 3 |

1 Visit 1/Visit 2 and Visit A/Visit B are defined in Section 6.2.1.

#### 5.1.1.3.1 Efficacy Endpoints

The primary efficacy endpoint is the change from baseline (CFB) to Week 6 in the percentage of catheterizations without a leaking accident as recorded in the 2-day urinary diary.

Distributions for the primary endpoint between participants treated with oxybutynin chloride gel in the two different types of treatment periods (Pre-Amendment 3 double-blind treatment period or Post-Amendment 3 open-label treatment period) of the study will be compared. Specifically, an exact two-sample Kolmogorov-Smirnov test will be used to compare the two distributions, with a p-value of 0.05 used as the threshold to reject the null hypothesis that the distributions for the two periods are the same.

If the distributions of the endpoint between these two periods are similar ($p \geq 0.05$), the primary analysis of the primary efficacy endpoint analysis will compare the difference between oxybutynin chloride gel and placebo in the Combined ITT population for the change from baseline in the percentage of catheterizations without a leaking accident at Week 6 using an analysis of covariance (ANCOVA) model with the baseline measure of the primary variable as the covariate and treatment group (active or placebo) as the factor.

If the distributions for the endpoint show a significant difference ($p < 0.05$) between these two periods, the data from the Pre-Amendment 3 double-blind treatment period and the data from the Post-Amendment 3 open-label treatment period will be analyzed separately as the primary analysis:

- For Pre-Amendment 3, the primary endpoint analysis will compare the difference between oxybutynin chloride gel and placebo in the Pre-Amendment 3 ITT population for the change from baseline in the percentage of catheterizations without a leaking accident at Week 6 using an ANCOVA model with the baseline measure of the primary variable as the covariate and treatment group as the factor.

- For Post-Amendment 3, a 2-sided one-sample t-test will be used on the primary endpoint to test for a significant difference from zero in the Post-Amendment 3 ITT population.

The analysis method which is not used as the primary analysis will serve as a supplementary analysis of the primary endpoint.

Secondary endpoints include the change from baseline to Week 6 of treatment in:

- average volume of urine collected per catheterization
- average volume of urine collected at first (morning awakening) catheterization
- average number of catheterizations per day

Analysis populations and methodologies for secondary endpoints will be handled similarly to the primary endpoint. For each secondary endpoint, an exact two-sample Kolmogorov-Smirnov test will be used to compare the two distributions, with a p-value of 0.05 used as the threshold to determine the main analysis method for that endpoint (i.e., the main analysis will use the combined ITT population if $p \geq 0.05$, and the main analysis will analyze the treatment periods separately if $p < 0.05$).

Efficacy variables will be analyzed as described in the following table. The urinary diary endpoints will be analyzed for the ITT and PP analysis populations at Week 6 (LOCF), and for ITT and PP analysis populations at each OC Visit. The pharmacodynamic endpoints will be analyzed for the ITT population.

**Table 5-12 Efficacy and Pharmacodynamic Analyses**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Percentage of catheterizations without a leaking accident | Change from baseline to Week 6 (or LOCF) calculated over 2 diary days | Pre-Amendment 3 Week 6 (LOCF) of double-blind period; Post-Amendment 3 Week 6 (LOCF) of open-label period; Combined ITT (LOCF) | CFB ANCOVA Pre-Amendment 3; CFB one-sample t-test Post-Amendment 3; CFB ANCOVA for Combined ITT |
| Percentage of catheterizations without a leaking accident | Raw value for Week 6 (or LOCF) calculated over 2 diary days | Pre-Amendment 3 Week 6 (LOCF) of double-blind period; Post-Amendment 3 Week 6 (LOCF) of open-label period | Continuous descriptives |
| Percentage of catheterizations without a leaking accident | Change from baseline to OC Visits (Week 2, Week 6) calculated over 2 diary days | Pre-Amendment 3 Week 2, Week 6 of double-blind period; Post-Amendment 3 Week 6 of open- | CFB ANCOVA Pre-Amendment 3; CFB one-sample t-test |

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| | | label period; Combined ITT (OC) | Post-Amendment 3; CFB ANCOVA for Combined ITT |
| Percentage of catheterizations without a leaking accident | Raw value for OC Visits (Week 0, Week 2, Week 6) calculated over 2 diary days | Pre-Amendment 3 Week 0, Week 2, Week 6 of double-blind period; Post-Amendment 3 Week 0, Week 6 of open-label period | Continuous descriptives |
| Average volume of urine collected at first (morning awakening) catheterization | Average change from baseline to Week 6 (or LOCF) calculated over 2 diary days | Pre-Amendment 3 Week 6 (LOCF) of double-blind period; Post-Amendment 3 Week 6 (LOCF) of open-label period; Combined ITT (LOCF) | CFB ANCOVA Pre-Amendment 3; CFB one-sample t-test Post-Amendment 3; CFB ANCOVA for Combined ITT |
| Average volume of urine collected at first (morning awakening) catheterization | Average raw value for Week 6 (or LOCF) calculated over 2 diary days | Pre-Amendment 3 Week 6 (LOCF) of double-blind period; Post-Amendment 3 Week 6 (LOCF) of open-label period | Continuous descriptives |
| Average volume of urine collected at first (morning awakening) catheterization | Average change from baseline for OC Visits (Week 2, Week 6) calculated over 2 diary days | Pre-Amendment 3 Week 2, Week 6 of double-blind period; Post-Amendment 3 Week 6 of open-label period; Combined ITT (OC) | CFB ANCOVA Pre-Amendment 3; CFB one-sample t-test Post-Amendment 3; CFB ANCOVA for Combined ITT |
| Average volume of urine collected at first (morning awakening) catheterization | Average Raw value for OC Visits (Week 0, Week 2, Week 6) calculated over 2 diary days | Pre-Amendment 3 Week 0, Week 2, Week 6 of double-blind period; Post-Amendment 3 Week 0, Week 6 of open-label period | Continuous descriptives |
| Average number of catheterizations per day | Average change from baseline to Week 6 (or LOCF) calculated over 2 diary days | Pre-Amendment 3 Week 6 (LOCF) of double-blind period; Post-Amendment 3 Week 6 (LOCF) of open-label period; Combined ITT (LOCF) | CFB ANCOVA Pre-Amendment 3; CFB one-sample t-test Post-Amendment 3; ANCOVA for Combined ITT |
| Average number of catheterizations per day | Average raw value for Week 6 (or LOCF) calculated over 2 diary days | Pre-Amendment 3 Week 6 (LOCF) of double-blind period; Post-Amendment 3 Week 6 (LOCF) of open-label period | Continuous descriptives |

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Average number of catheterizations per day | Average change from baseline for OC Visits (Week 2, Week 6) calculated over 2 diary days | Pre-Amendment 3 Week 2, Week 6 of double-blind period; Post-Amendment 3 Week 6 of open-label period; Combined ITT (OC) | CFB ANCOVA Pre-Amendment 3; CFB one-sample t-test Post-Amendment 3; CFB ANCOVA for Combined ITT |
| Average number of catheterizations per day | Raw value for OC Visits (Week 0, Week 2, Week 6) calculated over 2 diary days | Pre-Amendment 3 Week 0, Week 2, Week 6 of double-blind period; Post-Amendment 3 Week 0, Week 6 of open-label period | Continuous descriptives |
| Average volume of urine collected per catheterization (for Pre-Amendment 3 population only) | Change from baseline to Week 6 (or LOCF) calculated over 2 diary days | Pre-Amendment 3 Week 6 (LOCF) of double-blind period | CFB ANCOVA Pre-Amendment 3 |
| Average volume of urine collected per catheterization (for Pre-Amendment 3 population only) | Average raw value for Week 6 (or LOCF) calculated over 2 diary days | Pre-Amendment 3 Week 6 (LOCF) of double-blind period | Continuous descriptives |
| Average volume of urine collected per catheterization (for Pre-Amendment 3 population only) | Change from baseline for OC Visits (Week 2, Week 6) calculated over 2 diary days | Pre-Amendment 3 Week 2, Week 6 of double-blind period | CFB ANCOVA Pre-Amendment 3 |
| Average volume of urine collected per catheterization (for Pre-Amendment 3 population only) | Average raw value for OC Visits (Week 2, Week 6) calculated over 2 diary days | Pre-Amendment 3 Week 0, Week 2, Week 6 of double-blind period | Continuous descriptives |
| Maximal bladder capacity | Change from baseline to Week 6 (or LOCF) | Pre-Amendment 3 Week 6 (LOCF) of double-blind period; Post-Amendment 3 Week 6 (LOCF) of open-label period; Combined ITT (LOCF) | CFB ANCOVA Pre-Amendment 3; CFB one-sample t-test Post-Amendment 3; CFB ANCOVA for Combined ITT |
| Detrusor pressure at maximal bladder capacity | Change from baseline to Week 6 (or LOCF) | Pre-Amendment 3 Week 6 (LOCF) of double-blind period; Post-Amendment 3 Week 6 (LOCF) of open-label period; Combined ITT (LOCF) | CFB ANCOVA Pre-Amendment 3; CFB one-sample t-test Post-Amendment 3; CFB ANCOVA for Combined ITT |

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Maximum amplitude of involuntary detrusor pressure | Change from baseline to Week 6 (or LOCF) | Pre-Amendment 3 Week 6 (LOCF) of double-blind period; Post-Amendment 3 Week 6 (LOCF) of open-label period; Combined ITT (LOCF) | CFB ANCOVA Pre-Amendment 3; CFB one-sample t-test Post-Amendment 3; CFB ANCOVA for Combined ITT |
| Volume at first involuntary detrusor contraction | Change from baseline to Week 6 (or LOCF) | Pre-Amendment 3 Week 6 (LOCF) of double-blind period; Post-Amendment 3 Week 6 (LOCF) of open-label period; Combined ITT (LOCF) | CFB ANCOVA Pre-Amendment 3; CFB one-sample t-test Post-Amendment 3; CFB ANCOVA for Combined ITT |
| Presence (versus total absence) of involuntary detrusor contractions at > 15 cm H2O | Raw value at Week 6 (or LOCF) | Pre-Amendment 3 Week 6 (LOCF) of double-blind period; Post-Amendment 3 Week 6 (LOCF) of open-label period; Combined ITT (LOCF) | CMH test Pre-Amendment 3; Exact 95% CI Post-Amendment 3; CMH test for Combined ITT |

1 Weeks are defined in Section 6.2.1.

### 5.1.1.4 Safety Analyses

Safety analyses will be based on each safety population.

Baseline assessments for applicable safety endpoints defined as follows:

**Table 5-13 Safety Endpoint Baseline Definitions**

| Parameter | Description | Timing |
|---|---|---|
| • Clinical laboratory evaluations<br>• Vital signs<br>• Physical Examination<br>• Skin Assessments for Erythema | eCRF- or (standardized) vendor-provided assessments | Latest non-missing assessment on/before treatment start date |

#### 5.1.1.4.1 Study Treatment Exposure and Compliance

Study treatment exposure and compliance will be summarized by treatment group or oxybutynin chloride gel level, as applicable, and by visit and overall for each safety population as follows:

**Table 5-14 Study Treatment Summaries**

| Parameter | Description | Timing | Methodology |
|---|---|---|---|
| Study treatment exposure (days) | Date of last dose of the study drug minus Date of first dose of the study drug + 1 | Study Period within a Study Part[1] | Continuous descriptives |
| Categorical study treatment exposure | Number and percentage of participants exposed to treatment during each of the following intervals:<br>• Week (0, 1]<br>• Week (1, 2]<br>• Week (2, 3]<br>• Week (3, 4]<br>• Week (4, 5]<br>• Week (5, 6]<br>• Week (6, 7]<br>• Week (7, 8]<br>• Week (8, 9]<br>• Week (9, 10]<br>• Week (10, 11]<br>• Week (11, 12]<br>• Week (12, 13]<br>• Week (13, 14]<br>• Week >=14 | Study Period within a Study Part[1] | Categorical descriptives |
| Study treatment compliance (%) | Summary by period interval<br>Pre-Amendment 3:<br>$100 \times \frac{\text{\# of sachets dispensed} - \text{\# returned}}{\text{\# expected}}$<br>Post-Amendment 3:<br>$100 \times \frac{\text{\# of sachets taken}}{\text{\# expected}}$ | Study Period within a Study Part[1] | Continuous descriptives |

1 Study part refers to pre-amendment 3 and post-amendment 3; pre-amendment 3 has both open-label and double-blind periods, post-amendment 3 has only open-label period.

#### 5.1.1.4.2 Adverse Events

Adverse event summaries will be presented for each safety population as follows:

- Post-Amendment 3 open-label safety population: by oxybutynin chloride gel dose level and overall
- Pre-Amendment 3 double-blind safety population: by treatment group, treatment and dose level, and overall
- Pre-Amendment 3 open-label safety population: by oxybutynin chloride gel dose level and overall
- Combined open-label safety population: by oxybutynin chloride gel dose level and overall

Adverse event summaries will be done overall and also for each age, weight, and sex group.

The following adverse event (AE) terms are defined:

An AE will be considered as a treatment-emergent adverse event (TEAE) if the AE initially occurs or increases in intensity on or after the first dose of study drug in the study. An event that occurs more than 30 days after the last dose of study drug will not be considered as treatment-emergent.

**Table 5-15 AE Terms**

| Term | Description |
|---|---|
| Treatment-emergent | Double-blind period:<br>• First dose date of double-blind period ≤ event start date ≤ last dose date of double-blind period + 30 days if participant does not enter the 8-week open-label period; or<br>• First dose date of double-blind period ≤ event start date < first dose date of open-label period if participant enters the 8-week open-label period |
| | Open-label period:<br>• First start date of open-label period ≤ event start date ≤ last dose date of open-label period + 30 days |

AEs, encompassing abnormalities and surgeries reported as occurring after the Screening Visit, will be coded using MedDRA Version 19.1 or later. Unique participants reporting AEs in the following AE categories will be summarized for the groups defined above for each safety population as follows:

**Table 5-16 AE Summaries**

| Parameter | Description | Timing | Methodology |
|---|---|---|---|
| Overall summary | Overall summary only for the following category:<br>• Treatment-emergent AEs (TEAEs) | Study Period within Study Part[2,3] ; Combined open-label period | Categorical descriptives |
| TEAE | Overall summary and by SOC and PT | Study Period within Study Part[2,3] ; Combined open-label period | Categorical descriptives |
| TEAEs by severity | Overall summary and by SOC, PT, and intensity<br>• Participants categorized overall and within each SOC and PT for the most intense occurrence | Study Period within Study Part[2,3]; Combined open-label period | Categorical descriptives |
| TEAE by study treatment relationship | Overall summary and by SOC, PT, and study treatment relationship in descending order | Study Period within Study Part[2,3] ; Combined open-label period | Categorical descriptives |
| Serious TEAEs by study treatment relationship and severity | Overall summary and by SOC, PT, study treatment relationship and intensity<br>• Participants categorized overall and within each SOC and PT for the most intense occurrence | Study Period within Study Part[2,3] ; Combined open-label period | Categorical descriptives |
| TEAEs leading to premature discontinuation[1] | Overall summary and by SOC, PT and study treatment relationship | Study Period within Study Part[2,3] ; Combined open-label period | Categorical descriptives |

1 Participants who report ≥ 1 AE in the AE category and all AEs for those participants will be listed. SOCs will be sorted alphabetically; PTs will be sorted in descending frequency in the highest dose group.

2 Study part refers to pre-amendment 3 and post-amendment 3; pre-amendment 3 has both open-label and double-blind periods, post-amendment 3 has only open-label period.

3 AEs with onset more than 30 days after the last dose of study drug are excluded from analysis.

### 5.1.1.4.3 Clinical Laboratory Assessments

Clinical laboratory assessments will be summarized by treatment group, double-blind treatment/oxybutynin chloride gel sequence, or oxybutynin chloride gel only group, as applicable, and by analyte and visit for each safety population. Study Part is either Pre-Amendment 3 or Post-Amendment 3.

**Table 5-17 Clinical Laboratory Summaries**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Descriptives | Summary of change from baseline by laboratory category and parameter in SI units and analysis visit<br>• Parameters specified in Section 6.4.2.2 | Visit F[1] for Post-Amendment 3 and Visit 8 for Pre-Amendment 3 | CFB descriptives |
| Descriptives | Summary of raw values by laboratory category and parameter in SI units and analysis visit<br>• Parameters specified in Section 6.4.2.2 | Visits A and F[1] for Post-Amendment 3 and Visits 1 and 8 for Pre-Amendment 3 | Continuous descriptives |
| Shift from baseline[2] | Summary by laboratory category and parameter<br>• Low, normal, and high categories provided by the central laboratory<br>• Parameters specified in Section 6.4.2.2 | End of Period within a Study Part[2] | Shift analysis |

1 Pre-Amendment 3 Week 14 or End of Treatment within Pre-Amendment 3; Post-Amendment 3 Week 14 or End of Treatment within Post-Amendment 3

2 Study part refers to pre-amendment 3 and post-amendment 3; pre-amendment 3 has both open-label and double-blind periods, post-amendment 3 has only open-label period.

Laboratory assessments values meeting *any* of the PCS low or PCS high criteria specified in Section 6.4.2.1 will be identified as PCS in the laboratory data listing.

### 5.1.1.4.3.1 Potential Hy's Law

Potential Hy's Law criteria will be summarized by treatment group, double-blind treatment/oxybutynin chloride gel sequence, or oxybutynin chloride gel only group, as applicable, and visit for each open-label safety population as follows:

**Table 5-18 Potential Hy's Law Summaries**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Potential Hy's Law within 24-hour window | Postbaseline assessment of the following laboratory parameters based on blood draws collected within a 24-hour period:<br>• ALT or AST ≥ 3 × ULN and<br>• TBL ≥ 2 × ULN and<br>• ALP < 2 × ULN | Study Period within Study Part[1] | Categorical descriptives |
| Potential Hy's Law without window (e-DISH) | Postbaseline assessment of the following laboratory parameters at any time:<br>• Maximum ALT or AST ≥ 3 × ULN<br>• Maximum TBL ≥ 2 × ULN | Study Period within Study Part[1] | Categorical descriptives |

e-DISH = evaluation of drug-induced serious hepatotoxicity.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin.
ALP = alkaline phosphatase; ULN = upper limit of normal.

1 Study part refers to pre-amendment 3 and post-amendment 3; pre-amendment 3 has both open-label and double-blind periods, post-amendment 3 has only open-label period.

#### 5.1.1.4.4 Vital Signs

Vital signs will be summarized by treatment group, double-blind treatment/oxybutynin chloride gel sequence, or oxybutynin chloride gel only group, as applicable, and visit for each safety population as follows:

**Table 5-19 Vital Signs Summaries**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Descriptives | Summary of change from baseline by parameter and analysis visit<br>Parameters specified in Section 6.4.3.1 | Pre-Amendment 3 Weeks 1 to 6; Post-Amendment 3 Visits B, C, D, E, and F[1] | CFB descriptives |
| Descriptives | Summary of raw values by parameter and analysis visit<br>Parameters specified in Section 6.4.3.1 | Pre-Amendment 3 all double-blind visits; Post-Amendment 3 Visits A, B, C, D, E, and F[1] | Continuous CFB descriptives |
| Descriptives | Summary of raw values and change from baseline by parameter and analysis visit<br>Parameters specified in Section 6.4.3.1 | Combined open-label period | Continuous CFB descriptives |

1 Analysis visits defined in Section 6.2.2.

#### 5.1.1.4.5 Physical Examination

Physical examination assessments will be summarized for each safety population by double-blind treatment group or oxybutynin chloride gel only group, as applicable, and visit.

**Table 5-20 Physical Examination Summaries**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Each body system at a visit rated (Normal/Abnormal)[1] | Summary of number and percentage of subjects Normal at baseline who shifted to Abnormal post-baseline by parameter and analysis visit | Visits 8 and F[2], Combined open-label period | Categorical CFB descriptives |

1 The denominator for calculating the percentages will be based on the number of patients evaluated for a body system at the visit who were rated as Normal for the body system.

2 Analysis visits defined in Section 6.2.2.

#### 5.1.1.4.6 Skin Assessment for Erythema

Skin assessments for erythema will be summarized for each safety population by treatment group and visit for the Pre-Amendment 3 double-blind period and by oxybutynin chloride gel only and visit for the Pre-Amendment 3 open-label period, the Pre-Amendment double-blind and open-label periods combined, and the Post-Amendment 3 open-label period. Additionally, skin assessments for erythema will be summarized by visit for each of the above described.

**Table 5-21 Skin Assessment for Erythema Summaries**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Each erythema category (none, mild, moderate, severe) [1] | Summary by parameter and analysis visit | Visits C, D, E, and F[2] | Categorical CFB descriptives |

1 Participants who have non-missing assessments.
2 Analysis visits defined in Section 6.2.2.

## 5.1.1.5 Other Assessments

### 5.1.1.5.1 Anticholinergic Questionnaire

Anticholinergic symptom questionnaire data will be summarized for the Pre-Amendment 3 double-blind safety population by treatment group and visit and by treatment group, dose level, and visit for the double-blind period. Anticholinergic symptom questionnaire data will be summarized by oxybutynin chloride gel only and visit and by oxybutynin chloride gel only, dose level, and visit for the Pre-Amendment 3 open-label period and the Pre-Amendment 3 double-blind and open-label periods combined, and for the Post-Amendment 3 open-label period.

Additionally, shifts from baseline for each question will be provided for all evaluable shifts. An evaluable shift is one where both the baseline evaluation and on-treatment evaluations are recorded.

**Table 5-22 Anticholinergic Questionnaire Summaries**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Each question on the questionnaire[1] overall and by age group and sex | Categorical summary of number and percentage of participants in a response category (no, mild, tolerable, or intolerable, applicable) by question and analysis visit; shift tables summarizing the shift in categorical response from baseline to each post-baseline visit (for Pre-Amendment 3 and also for Post-Amendment 3) | Pre-Amendment 3 Weeks 0, 6, and 14; Post-Amendment 3 Visits B, C, D, E, and F[2] | Categorical descriptives |

1 Participants who have non-missing assessments.
2 Analysis visits defined in Section 6.2.2.

### 5.1.1.5.2 Vision Questionnaire

Visit symptom questionnaire data will be summarized for the Post-Amendment 3 Open-Label Safety Population by visit overall and for each dose level.

**Table 5-23 Vision Questionnaire Summaries**

| Endpoint | Description | Timing | Methodology |
|---|---|---|---|
| Each question on the questionnaire (yes, no)[1] | Summary by question and analysis visit | Post-Amendment 3 Visits B, C, D, E, and F[2] | Categorical descriptives |

1 Participants who have non-missing assessments.
2 Analysis visits defined in Section 6.2.2.

### 5.1.1.6 Subgroup Analyses

The primary and secondary efficacy LOCF data analyses will be analyzed separately for each group for each ITT population, as appropriate:

Age Group:

- 3 to < 6 years
- 6 to < 12 years
- 12 to < 17 years

Weight Category by Age Group:

- <=18 kg and 3 to < 6 years
- >18 kg and 3 to < 6 years
- <=25 kg and 6 to < 12 years
- >25 kg and 6 to < 12 years
- <=50 kg and 12 to <17 years
- >50 kg and 12 to <17 years

Sex:

- Male
- Female

Here the same analysis methodologies as the primary and secondary analyses will be applied for the ITT populations (See Section 5.1.1.1.3, CFB ANCOVA). ANCOVA will be performed for each subgroup if the sample size available is at least 14 subjects. The Wilcoxon signed-rank test will be used when the one-sample t-test is not valid (See Section 5.1.1.1.3, CFB one -sample t-test).

Additionally, analysis of other important subgroups may be provided as appropriate.

### 5.1.1.7 Interim Analyses

Not applicable.

### 5.1.2 Determination of Sample Size

Sample size was calculated for the protocol as originally designed (Pre-Amendment 3: double-blind, placebo-controlled treatment period followed by an open-label extension) as follows:

This study was planned to include a minimum of 96 pediatric participants aged 6 to < 17 years who have a diagnosis of detrusor overactivity associated with a neurological condition. The sample size was selected to provide an adequate number of participants to evaluate the safety and efficacy of oxybutynin chloride gel treatment in a pediatric population. Participants were randomized in a 1:1 fashion to oxybutynin chloride gel or placebo within each stratification level, which were based on age, weight, and sex. Estimates for the average change from baseline (CFB) in the percentage of catheterizations without a leaking accident as well as the standard deviation for this variable were taken from oxybutynin TDS in Study O03010. Assuming a common standard deviation of 28 for the CFB in the percentage of catheterizations without a leaking accident, a difference between treatment groups of 20 (assuming average for oxybutynin chloride gel = 25 and average for placebo = 5), and n = 48 participants per treatment group, there is 93% power to detect a statistically significant difference between treatment groups. Based on discontinuation rates from Study O03010, if we assume a 10% dropout rate, then there is 90% power to detect a statistically significant difference between treatment groups.

The open-label study (participants enrolled Post-Amendment 3) will include a minimum of 25 pediatric participants aged 3 to < 17 years (efforts will be made to enroll a greater number of participants aged 3 years to < 6 years) who have a diagnosis of detrusor overactivity associated with a neurological condition. This sample size is expected to provide a minimum of 10 participants with 14 weeks of exposure.

## 5.2 Changes in the Conduct of the Study or Planned Analyses

At the time of writing this SAP, there were no changes in study conduct from what is described in the protocol and protocol amendments. Changes to planned analyses from what was described in the protocol are detailed in this SAP as described in Section 5.2.2 below.

### 5.2.1 Changes in the Conduct of the Study

Not applicable.

### 5.2.2 Changes to Analyses Prior to Database Lock

| Version | Date | Summary |
|---|---|---|
| 1.0 | 24 Oct 2017 | Original version |
| 2.0 | 28 Mar 2022 | ○ Exact (Clopper-Pearson) 95% CI, Exact unconditional 95% CI using the score statistic, and Cochran-Mantel-Haenszel (CMH) was added in Table 5-2 to analyze binary urodynamic variable (Presence (versus total absence) of involuntary detrusor contractions at > 15 cm H2O)<br>○ CFB Mixed Model was deleted from Table 5-2. All CFB Mixed model analyses have been replaced with CFB ANCOVA as reflected in Table 5-12<br>○ Study part was removed as a factor from the CFB ANCOVA models<br>○ Details of how urodynamic assessments will be analyzed have been added in Table 5-12<br>○ Section 5.1.1.2 was modified to clarify analysis populations presented in demographics tables.<br>○ Exact Kolmogorov-Smirnov test was added in Table 5-2 to compare whether distributions of efficacy endpoints between patients treated with oxybutynin chloride gel in the two parts (Pre-Amendment 3 and Post-Amendment 3) of the study are the same<br>○ Section 5.1.1.3.1 was modified to provide details on how efficacy endpoints will be analyzed based on whether the distributions of efficacy endpoints between patients treated with oxybutynin chloride gel in the two parts (Pre-Amendment 3 and Post-Amendment 3) of the study were the same or not<br>○ Updated Table 5-15 definition of treatment-emergent adverse events in double-blind period to distinguish between participants who enter the 8-week open-label period from those that do not |

# 6. Data Handling and Analysis Conventions

## 6.1 Study Treatment Conventions

### 6.1.1 Analysis Days

Treatment days are defined as follows:

**Table 6-1 Analysis Day Definitions**

| Term | Description |
|---|---|
| Treatment Day | Double-Blind<br>Relative to first dose date in double-blind phase if analysis date ≥ first dose date in double-blind phase:<br>• Day = analysis date – first dose date in double-blind phase + 1<br>  ○ Day 1 =first dose date in double-blind phase<br>If analysis date < first dose date in double-blind phase:<br>• Day = analysis date – first dose date in double-blind phase<br>  ○ Day -1 = day before first dose date in double-blind phase<br>  ○ There is no Day 0<br><br>Open-Label<br>Relative to first dose date in open-label phase if analysis date ≥ first dose date in open-label phase:<br>• Day = analysis date – first dose date in open-label phase + 1<br>  ○ Day 1 =first dose date in open-label phase<br>If analysis date < first dose date in open-label phase:<br>• Day = analysis date – first dose date in open-label phase<br>  ○ Day -1 = day before first dose date in open-label phase<br>  ○ There is no Day 0 |

### 6.1.2 Missing/Incomplete Treatment End Date

If the investigator is unable to provide the treatment end date, treatment end date will be imputed to the last available dosing record date.

## 6.2 Analysis Visit Windows

### 6.2.1 Efficacy

The analysis visit windows for efficacy endpoints during Post-Amendment 3 open-label period are defined as follows:

**Table 6-2 Efficacy Analysis Visit Definitions for Pre-Amendment 3 Double-Blind Treatment Period**

| Analysis Phase | | Analysis Visit (Derived) | Study Visit (CRF) | Window |
|---|---|---|---|---|
| Treatment | Double-Blind Period | Baseline | Visit 1/Visit 2 | Treatment Day ≤ 1 |
| | | Week 2 | Visit 4 | Treatment Day [2, 28] |
| | | Week 6 | Visit 6 | Treatment Day [29, X[1]] if patients enters open label period; Treatment Day ≥ 29 otherwise |

1 X = First dose date of open label period – first dose date of double blind period + 1.

**Table 6-3 Efficacy Analysis Visit Definitions for Post-Amendment 3 Open-Label Treatment Period**

| Analysis Phase | Analysis Visit (Derived) | Study Visit (eCRF) | Window |
|---|---|---|---|
| Treatment | Baseline | Visit A/Visit B | Treatment Day ≤ 1 |
| | Week 6 | Visit D | Treatment Day ≥ 29of open-label treatment |

## 6.2.2 Safety and Other Assessments

The analysis visit windows for safety and other assessment endpoints are defined as follows:

**Table 6-4 Safety Analysis Visit Definitions for Pre-Amendment 3**

| Analysis Phase | | Analysis Visit (Derived) | Study Visit (CRF) | Window |
|---|---|---|---|---|
| Treatment | Double-Blind Period | Baseline | Visit 1/ Visit 2 | Treatment Day ≤ 1 |
| | | Week 1 | Visit 3 | Treatment Day [2, 11] |
| | | Week 2 | Visit 4 | Treatment Day [12, 21] |
| | | Week 4 | Visit 5 | Treatment Day [22, 35] |
| | | Week 6 | Visit 6 | Treatment Day [36, X[1]] if patients enters open label period; Treatment Day ≥ 36 otherwise |
| | Open-Label Period | Week 8 | Visit 7 | Treatment Day [2, 35] of open-label treatment |
| | | Week 14 | Visit 8/ET | Treatment Day ≥ 36 of open-label treatment |

1 X = First dose date of open label period – first dose date of double blind period + 1.

**Table 6-5 Safety Analysis Visit Definitions for Post-Amendment 3 Open-Label Treatment Period**

| Analysis Phase | Analysis Visit (Derived) | Study Visit (eCRF) | Window |
|---|---|---|---|
| Treatment | Baseline | Visit A/Visit B | Treatment Day ≤ 1 |
| | Week 2 | Visit C | Treatment Day [2, 28] |
| | Week 6 | Visit D | Treatment Day [29, 56] |
| | Week 10 | Visit E | Treatment Day [57, 84] |
| | Week 14 | Visit F/ET | Treatment Day ≥ 85 |

The following general conventions for repeated or unscheduled assessments will apply unless otherwise specified:

- The latest non-missing assessment within any analysis window will be flagged as the analysis value for any summaries by analysis visit
- All postbaseline assessments will be considered for PCS categorization
- All assessments will be included in respective listings

## 6.3 Missing/Incomplete Date Conventions

Dates may be imputed with year, month, and day values under certain scenarios:

**Table 6-6 Imputation Scenarios**

| Scenario | Complete | | | Imputable |
|---|---|---|---|---|
| | Year | Month | Day | |
| 1 | Yes | Yes | Yes | Complete |
| 2 | Yes | Yes | — | Yes |
| 3 | Yes | — | Yes | No[1] |
| 4 | Yes | — | — | Yes |
| 5 | — | Yes | Yes | No[1] |
| 6 | — | Yes | — | No[1] |
| 7 | — | — | Yes | No[1] |
| 8 | — | — | — | Yes |

1 Not allowed per database design.

Dates will be imputed initially toward a specified target date for imputable scenarios 2, 4, and 8, and adjusted against the latest reasonable dates. The initial imputed date is determined by the following algorithm:

**Table 6-7 Initial Imputed Date Algorithm**

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

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

### 6.3.1 Missing/Incomplete AE Start Date

AE start dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment start date
- Complete end date

### 6.3.2 Missing/Incomplete Medication Start Date

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

- Initial imputed date, where target date = Treatment start date – 1
- Complete end date

### 6.3.3 Missing/Incomplete AE/Medication End Date

AE and medication end dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Last dose date + 30
- Death date

## 6.4 Safety Endpoint Conventions

### 6.4.1 Adverse Events

#### 6.4.1.1 Missing Intensity or Relationship

If the investigator is unable to provide the actual values, the following imputations will be applied:

**Table 6-8 Missing AE Intensity and Relationship Imputation Algorithms**

| Missing Value | Imputation | Timing |
|---|---|---|
| Intensity | Mild | Screening Period |
| | Severe | Treatment Period |
| Relationship | — | Screening Period |
| | Related | Treatment Period |

## 6.4.2 Clinical Laboratory Assessments

### 6.4.2.1 Potentially Clinically Significant Criteria

Laboratory assessments values meeting *any* of the following PCS low or PCS high criteria will be identified as PCS in the laboratory data listing:

**Table 6-9 Clinical Laboratory PCS Criteria**

| Category | Parameter | SI Unit | PCS Criteria | |
|---|---|---|---|---|
| | | | PCS Low | PCS High |
| Chemistry | Albumin | g/L | < 0.9 × LLN | > 1.1 × ULN |
| | Alanine aminotransferase | U/L | — | ≥ 3.0 × ULN |
| | Aspartate aminotransferase | U/L | — | ≥ 3.0 × 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, fasting | mmol/L | < 0.8 × LLN | > 1.2 × 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 |
| Hematology | Hematocrit | Ratio | < 0.9 × LLN | > 1.1 × ULN |
| | Hemoglobin | g/L | < 0.9 × LLN | > 1.1 × 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 | pH | — | < 0.9 × LLN | > 1.1 × ULN |
| | Specific gravity | — | — | > 1.1 × ULN |

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

### 6.4.2.2 Continuous Descriptives and Shift Table Parameters

The following laboratory parameters will be summarized:

**Table 6-10 Clinical Descriptive and Shift Table Parameters**

| Category | Parameters | | | |
|---|---|---|---|---|
| Hematology | Platelet count | ***RBC Indices:*** | ***WBC count with Differential:*** | |
| | RBC count | MCV | Neutrophils | |
| | Hemoglobin | MCH | Lymphocytes | |
| | Hematocrit | %Reticulocytes | Monocytes | |
| | | | Eosinophils | |
| | | | Basophils | |
| Chemistry | BUN | Potassium | AST (SGOT) | Total bilirubin |
| | Creatinine | Sodium | ALT (SGPT) | Total protein |
| | Glucose [fasting or nonfasting will be indicated] | Calcium | Alkaline phosphatase | |

#### 6.4.2.3 Character Values

Character values (eg, < 5, negative) will be reviewed prior to database lock and converted to numeric for analysis as appropriate. These conversions will be documented in the ADaM specifications.

### 6.4.3 Vital Signs

#### 6.4.3.1 Continuous Descriptives Parameters

The following vital sign parameters will be summarized:

**Table 6-11 Vital Sign Descriptive Parameters**

| Parameters | | |
|---|---|---|
| Systolic BP | Respiratory rate | Weight (Screening only) |
| Diastolic BP | Temperature | BMI (Screening only) |
| Pulse rate | | |

BP = blood pressure.

## 6.5 Imputed Value Listing Conventions

In general, listings will present the actual partial or missing values rather than the imputed values that may be used in endpoint derivation. In instances where imputed values will be presented, imputed values will be flagged. Actual rules will be fully defined in the table, figure, and data listing specification document.

# Appendix 1 Schedule of Events for Pre-Amendment 3

## Appendix 1 Schedule of Events

| *Evaluation:* | | Treatment Period | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Screening Period | Double-Blind Placebo-Controlled | | | | | Open-Label Safety | |
| | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | Visit 8/ ET |
| | | Week 0 | Week 1 | Week 2 | Week 4 | Week 6 | Week 8 | Week 14 |
| Informed Consent | X | | | | | | | |
| I/E Criteria | X | X | | | | | | |
| Medical History | X | X | | | | | | |
| Concomitant Medication | X | X | X | X | X | X | X | X |
| Physical Examination | X | | | | | | | X |
| Height and Weight | X | | | | | | | |
| Vital Signs | X | X | X | X | X | X | X | X |
| 12-Lead ECG | X | | | | | | | |
| Serum Chemistries | X | | | | | | | X |
| Hematology | X | | | | | | | X |
| Urinalysis | X | X[2] | | | | | | X |
| Urine Culture | X | | | | | | | |
| Urine pregnancy test[1] | X | | | | | X | | X |
| Urodynamics | | X | | | | X | | |
| Dispense 2-day Urinary Diary | X | | X | | X | | | |
| Collect 2-day Urinary Diary | | X | | X | | X | | |
| Skin Tolerability Assessment | | | X | X | X | X | X | X |
| Adverse Event Assessment | | | X | X | X | X | X | X |
| Anticholinergic Questionnaire | | X | | | | X | | X |
| Collect PK Sample& Record Date/Time | | | X | X | X | X | | |
| Dose Titration (if necessary) | | | | X | | | X | |
| Randomization | | X | | | | | | |
| Test Article Dispensing | | X | | X | | X | X | |
| Test Article Accountability | | | | X | | X | X | X |

[1] Urine pregnancy test will only be performed for females of childbearing potential.

[2] A urine sample for on-site urinalysis to determine presence of bacterial infection will be collected.

Note that this table is found in Appendix 1 of OG09002 Protocol Amendment 2, Schedule of Events (Watson Laboratories, Inc. dated 25 June 2012).