1 TITLE PAGE

Clinical Study Protocol: OG09002

Study Title: 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

Study Number: OG09002

Study Phase: 4

Product Name: Oxybutynin Chloride 10% Gel

IND Number: 67,126

Indication: Detrusor Overactivity Associated with a Neurological Condition in Pediatric ***Patients***

Sponsor:
AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Sponsor's Responsible* Medical *Officer:
[redacted] ***M.D., PH.D.***
AbbVie Inc. [redacted]
1 North Waukegan Road, North Chicago, IL 60064
Off: [redacted] ***Fax:*** [redacted] ***Mobile:*** [redacted]
Email: [redacted]

Date	
Original Protocol:	01 September 2010
Protocol Amendment 1:	24 November 2010
Protocol Amendment 2:	25 June 2012
Protocol Amendment 3:	27 September 2016
Protocol Amendment 4:	***31 October 2022***

Confidentiality Statement

Investigator Statement

I have read this protocol and understand its requirements. I agree to conduct the study as described herein and will not deviate from the protocol without prior written approval from the sponsor or designee. Any protocol changes must be made by written amendment to the protocol and will not be implemented until approved by the institutional review board or ethics committee.

_____ _____

Principal Investigator Signature Date

_____

Printed Name

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	*31 Oct 2022*
Amendment 3	*27 Sep 2016*
Amendment 2	*25 Jun 2012*
Amendment 1	*24 Nov 2010*
Original Protocol	*01 Sep 2010*

Amendment 4 ([redacted])

The purpose of Global Protocol Amendment 4 is to include administrative change, to update recent changes in Sponsor Contact and Medical Contact/TAMD for the study and information on the Contact Page updating email and phone number to address Safety concerns.

The following is a summary of changes made in Global Protocol Amendment 4. Strikethrough text denotes text removed and bolded text denotes added text. Additional administrative edits were also made, but not specifically noted (eg, corrected spelling, punctuation, grammar, abbreviation, and style errors) including global edits required for consistency.

Protocol Section(s)	Description of Changes	Rationale for Changes
Title Page	• Updated recent changes in Sponsor Contact and Medical Contact/TAMD for the study and information on the Contact Page. • Following information is removed ~~Allergan Sales, LLC~~ ~~2525 Dupont Drive~~ ~~Irvine, CA 92612~~ [redacted] ~~MD~~ ~~Medical Safety Physician~~ ~~Allergan Sales, LLC~~ ~~Office:~~ [redacted] ~~Email:~~ [redacted] ~~Secondary Contact:~~ [redacted] ~~MD~~ ~~Director, Medical Safety Physician~~ ~~Allergan, S.p.A.~~ ~~Email:~~ [redacted] • Added the following information **AbbVie Inc.** **1 North Waukegan Road** **North Chicago, IL 60064** [redacted] **M.D., PH.D.** **AbbVie Inc.** [redacted] **1 North Waukegan Road, North Chicago, IL 60064** **Off:** [redacted] **Fax:** [redacted] **Mobile:** [redacted] **Email:** [redacted]	• To reflect current information

Investigator and Study Administrative Structure	• Updated recent changes in Sponsor Contact, Clinical Scientist, Biostatistician, and Medical Safety Physician information under section 6. • Following information is removed Sponsor: ~~Allergan Sales, LLC~~ ~~2525 Dupont Drive~~ ~~Irvine, California 92612~~ Clinical Scientist: [redacted] ~~PhD~~ ~~Associate Director, Clinical Development~~ ~~Allergan Sales, LLC~~ Biostatistician: [redacted] ~~PhD~~ ~~Director, Biostatistics~~ ~~Allergan Sales, LLC~~ Medical Safety Physician: [redacted] ~~MD~~ ~~Allergan Sales, LLC~~ ~~Mobile:~~ [redacted] ~~Email:~~ [redacted] [redacted] ~~MD~~ ~~Allergan S.p.A.~~ ~~Email:~~ [redacted] ~~Email: IR-Clinical-SAE@Allergan.com~~ • Added the following information Sponsor: **AbbVie Inc.** **1 North Waukegan Road** **North Chicago, IL 60064** Therapeutic Area Scientific Director: [redacted] **PharmD** [redacted] **AbbVie Inc.**	• To reflect current information

Protocol Section(s)	Description of Changes	Rationale for Changes
	Biostatistician: [redacted] **PhD** **Senior Manager, Biostatistics** **AbbVie Inc.** Medical Safety Physician: [redacted] **MD., PhD** **AbbVie Inc.** [redacted] **1 North Waukegan Road, North Chicago, IL 60064** **Off:** [redacted] **Fax:** [redacted] **Mobile:** [redacted] **Email:** [redacted]	

Protocol Section(s)	**Description of Changes**	**Rationale for Changes**
Immediate Reporting of Serious Adverse Events and Events of Special Interest	• Updated changes in reporting SAE under section 9.7.1.5. • Following information is removed Fax the SAE Form for Clinical Trials to ~~Allergan n Sales, LLC~~. Global fax number for SAE or Pregnancy Reporting: 1-714-796-9504 (backup fax 1-714-246-5295) or email it to IR-Clinical-SAE@~~allergan~~.com. In case of fax failure or the site does not receive confirmation of receipt of the fax, the site must email the report to IR-Clinical-SAE@~~allergen~~.com. • Added the following information Fax the SAE Form for Clinical Trials to **AbbVie Inc**. Global fax number for SAE or Pregnancy Reporting: 1-714-796-9504 (backup fax 1-714-246-5295) or email it to IR-Clinical-SAE@**abbvie**.com. In case of fax failure or the site does not receive confirmation of receipt of the fax, the site must email the report to IR-Clinical-SAE@**abbvie**.com.	• To reflect current information

Protocol Section(s)	Description of Changes	Rationale for Changes
Medical Emergencies and Emergency Protocol Deviations	• Updated recent changes to Medical Safety Physician information under section 9.7.1.7. • Following information is removed Primary Contact: [redacted] ~~MD~~ ~~Medical Safety Physician~~ ~~Allergan Sales, LLC~~ ~~Mobile:~~ [redacted] ~~Email:~~ [redacted] Secondary Contact: [redacted] ~~MD~~ ~~Director, Medical Safety Physician~~ ~~Allergan S.p.A.~~ ~~Email:~~ [redacted] Medical emergency call center: 1-800-503-8745 Global fax for SAEs and pregnancy reports: 1-714-796-9504 (backup fax: 1-714-246-5295) ~~Email: IR-Clinical-SAE@allergan.com~~ • Added the following information Primary Contact: [redacted] **M.D., PH.D.** **AbbVie Inc.** [redacted] **1 North Waukegan Road, North Chicago, IL 60064** **Off:** [redacted] **Fax:** [redacted] **Mobile:** [redacted] **Email:** [redacted] Medical emergency call center: 1-800-503-8745 Global fax for serious adverse events or pregnancy reports: 1-714-796-9504 (backup fax: 1-714-246-5295) **Email: IR-Clinical-SAE@abbvie.com**	• To reflect current information

2 SYNOPSIS

Sponsor:
AbbVie Inc.

Name of Finished Product:
oxybutynin chloride gel

Name of Active Ingredient:
oxybutynin chloride

Study Title:
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

Study Number:
OG09002

Study Phase: Phase 4

Two-part Study:

This study will be conducted in 2 parts, Pre-Amendment 3 and Post-Amendment 3, as follows:

- Pre-Amendment 3: A double-blind, randomized, placebo-controlled treatment study with open-label extension. Patients will be enrolled into the 6-week placebo-controlled treatment followed by an 8-week open-label treatment phase.
- Post-Amendment 3: An open-label treatment study. Patients will be enrolled in a 6-week open-label treatment phase. A portion of enrolled patients will receive an additional 8 weeks of open-label treatment for a total of 14 weeks of open-label treatment.

Primary Objectives:
The primary objectives are:

- Pre-Amendment 3: To evaluate the efficacy of daily treatment with oxybutynin chloride gel compared to placebo in pediatric patients during the first 6 weeks of a 14-week treatment period.
- Post-amendment 3: To evaluate the efficacy of daily treatment with oxybutynin chloride gel in pediatric patients during the first 6-weeks of a 14-week open-label treatment period.

Secondary Objectives (*for Pre-Amendment 3 and Post-Amendment 3*):
The secondary objectives are to evaluate the pharmacokinetics, pharmacodynamics, safety, and skin tolerability of ***oxybutynin chloride gel*** in pediatric patients.

Study Design:
This study was initiated as a double-blind, placebo-controlled study with an open-label extension, and amended to enroll patients under only open-label treatment. Prior to Amendment 3, patients aged 6 years to < 17 years were randomly assigned 1:1 to receive double-blind oxybutynin chloride gel or placebo gel for 6 weeks, followed by an open-label, 8-week period to generate safety data. All patients began treatment with 0.75 g of gel/day for 2 weeks. Patients then returned to the clinic 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. Patients continued blinded treatment for 4 additional weeks until the end of the double-blind treatment period.

Post-Amendment 3, the study dose-titration study in pediatric patients, ages 3 years to < 17 years, with detrusor overactivity associated with a neurological condition. Efforts will be made to enroll a greater number of patients from the ages of 3 years to < 6 years. Patients must be suitable candidates for anticholinergic therapy and must be using clean intermittent catheterization (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. No changes were made in the starting dose, compared to the Pre-Amendment 3 study design, in that all patients will begin treatment with 0.75 g of gel/day for 2 weeks. Patients 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. Patients 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.

Study Population:
Pre-Amendment 3 included pediatric patients, from ages 6 years to < 17 years, who had a diagnosis of detrusor overactivity associated with a neurological condition and were using CIC to control bladder function. These patients were enrolled into the 6-week placebo-controlled treatment plus an 8-week open-label treatment phase of the study. Post-Amendment 3 enrollment will include pediatric patients from ages 3 years to < 17 years, who have a diagnosis of detrusor overactivity associated with a neurological condition and are using CIC to control bladder function, with an enrollment of a minimum of 25 patients. These patients will be enrolled in a 14-week open-label treatment phase (approximately 10 patients are expected to complete the 14 weeks).

Test Product, Dose, and Mode of Administration:
Oxybutynin chloride gel, 0.5 g, 0.75 g (starting dose for Pre- and Post-Amendment 3), or 1 g sachets, applied transdermally once daily to dry intact skin.

Comparator Product:

For Pre-Amendment 3: placebo gel

For Post-Amendment 3: no comparator

Duration of Treatment:

For Patients Enrolled Pre-Amendment 3: A 6-week placebo-controlled treatment period followed by an 8-week open-label period

For Patients Enrolled Post-Amendment 3*:* A 14-week open-label treatment period

Efficacy Assessment:
The primary efficacy endpoint is the change from baseline (CFB) to Week 6 of treatment or to the last observation carried forward (LOCF) in percentage of catheterizations without a leaking accident as recorded in the 2-day urinary diary.

Secondary endpoints include the CFB to Week 6 of treatment in the following:

Urinary diary endpoints (calculated from the 2-day urinary diary data):

- Average volume of urine collected per catheterization (for Pre-Amendment 3 population only)
- Average volume of urine collected at first (morning awakening) catheterization
- Average number of catheterizations per day

Pharmacodynamic Assessments:
Pharmacodynamics will be assessed for treatment under the Pre-Amendment 3 double-blind phase, treatment under the Post-Amendment 3 open-label study, and both groups where appropriate. Pharmacodynamics will be based on urodynamic testing. The following parameters will be evaluated:

- Maximal bladder capacity
- Detrusor pressures at maximum bladder capacity
- Maximum amplitude of involuntary detrusor contractions
- Volume at first involuntary detrusor contraction
- Presence (versus total absence) of involuntary detrusor contractions at > 15 cm H20

Safety Assessments:
Safety will be evaluated by monitoring adverse events, physical examinations, vital signs, and clinical laboratory evaluations including hematology, serum chemistries and urinalysis, assessing for local skin erythema at the application site, and visual assessments. The investigator will assess vital signs, adverse events, skin erythema, complete the anticholinergic questionnaire, and the vision symptom assessment questionnaire. Analyses and summaries will be performed under the Pre-Amendment 3 double-blind phase, the Pre-Amendment 3 open-label phase, and the Post-Amendment 3 open-label phase, with groups aggregated where appropriate.

Other Evaluations:
[redacted]

Statistical Methods:
All efficacy, safety, and other evaluation data will be summarized using descriptive statistics for continuous variables and frequency distributions for categorical variables.

The primary endpoint analysis will compare the difference between oxybutynin chloride gel (combined from Pre-Amendment 3 and Post-Amendment 3) and placebo in the change from baseline in the percentage of catheterizations without a leaking accident at Week 6 (LOCF) for the intent-to-treat (ITT) population using an analysis of covariance model with the baseline measure of the primary variable as the covariate and treatment group as factor. Analyses for secondary endpoints will use similar analysis of covariance models to compare differences between the treatment groups for the change from baseline to Week 6 (LOCF) for the ITT population.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	***adverse event***
ANCOVA	analysis of covariance
CFB	change from baseline
CFR	Code of Federal Regulations
CIC	clean intermittent catheterization
DDAVP	***desmopressin***
DEO	N-desethyloxybutynin
EC	ethics committee
ECG	electrocardiogram
eCRF	***electronic case report form***
ET	early termination
FDA	Food and Drug Administration
GCP	good clinical practice
HEENT	head, ears, eyes, nose, throat
HIPAA	Health Insurance Portability and Accountability Act
ICF	***informed consent form***
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	***identification***
IND	investigational new drug application
IRB	institutional review board
ITT	intent-to-treat
IVRS	interactive voice response system
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NF	***National Formulary***
OC	observed cases
PHI	protected health information
PK	pharmacokinetic
PP	per protocol
SAE	***serious adverse event***
TDS	transdermal system
ULN	upper limit of the normal range
US***P***	United States ***Pharmacopeia***

5 ETHICS

5.1 Institutional Review Board or Ethics Committee

The protocol and supporting documents for this study will be reviewed and approved by an appropriately constituted institutional review board (IRB) or ethics committee (EC) prior to study initiation.

All reviews and approvals will be in accordance with GCP as contained in the ICH guidelines (E6) and US CFR governing IRBs (Title 21, Part 56).

A letter from the IRB or EC documenting approval of the investigator (who must be identified by name), the protocol (must be identified by title), and the patient consent form must be received by the sponsor or its designee prior to study initiation. A progress report will be submitted by the investigator to the IRB or EC at intervals specified by the IRB or EC, but not less than annually. A copy of this progress report will be sent to the sponsor. After completion of the study, the investigator will submit a signed clinical safety summary of the study to the IRB or EC.

5.2 Ethical Conduct of Study

The study will be conducted in accordance with GCP as contained in ICH guidelines and US CFR governing the protection of human patients (Title 21, Part 50) and the obligations of clinical investigators (Title 21, Part 312.60 through 312.69). The study will also be conducted in accordance with the World Medical Association Declaration of Helsinki and all amendments.

The sponsor is responsible for the ongoing safety evaluation of the study treatment and will expedite the notification of all participating investigators and regulatory authorities of findings that are both serious and unexpected and/or that could adversely affect the safety of patients or the conduct of the study, or alter an IRB's or EC's approval to continue the study.

5.3 Patient Information and Consent

The investigator will ensure that each patient will provide assent (if applicable and according to IRB regulations) and their parent(s) or legal guardian(s) will sign the written informed consent form in accordance with applicable regulations.

Patients and their parent(s) or legal guardian(s) will be interviewed at the initial ***S***creening ***V***isit by qualified staff at the site and will be provided with a full description of the nature and purpose of the study. The patients and their parent(s) or legal guardian(s) will be given adequate time to consider the risks associated with participation in the study. Each patient will provide assent (if applicable and according to IRB regulations), and their parent(s) or legal guardian(s) will provide written informed consent prior to participating in any study procedures. The original signed consent forms will be retained on file at the clinical sites and a copy will be given to the patient. Case histories (patient charts) will also document that informed consent was obtained prior to the patient's participation in the study.

5.4 Authorization to Disclose Protected Health Information

If required under HIPAA regulations, patients and their parent(s) or legal guardian(s) will be informed of the following information:

- The sponsor of the study
- Any contractors that may be involved in the study
- The purpose of the protected health information (PHI) being collected
- The possibility that the PHI may be re-disclosed
- The duration of the authorization
- The patient's and parent's or legal guardian's rights to revoke the authorization; and
- The right of the patient and parent(s) or legal guardian(s) to refuse signature and limit access to PHI during the conduct of the trial (US CFR Title 45, Parts 160 and 164)

Authorization to disclose PHI must be obtained before the patient enters the study.

6 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

AbbVie Inc. is the sponsor of this study. On the approval date of this amended protocol, the administrative structure and the external organizations supporting the study were as follows:

Sponsor:	***AbbVie Inc.*** ***1 North Waukegan Road*** ***North Chicago, IL 60064***
Therapeutic Area Scientific Director:	[redacted] ***PharmD*** ***Director, Clinical Development Specialty*** ***AbbVie Inc.***
Biostatistician:	[redacted] ***PhD*** ***Senior Manager, Biostatistics*** ***AbbVie Inc.***
Medical Safety Physician:	[redacted] ***MD., PhD*** ***AbbVie Inc.*** [redacted] ***1 North Waukegan Road, North Chicago, IL 60064*** ***Off:*** [redacted] ***Fax:*** [redacted] ***Mobile:*** [redacted] ***Email:*** [redacted] ***Medical emergency call center: 1-800-503-8745*** ***Global fax for serious adverse events or pregnancy reports: 1-714-796-9504*** ***(backup fax: 1-714-246-5295)*** ***Email: IR-Clinical-SAE@abbvie.com***
Clinical Laboratory:	ACM Central Laboratories 160 Elmgrove Park Rochester, NY 14624 +1 866 405 0400
Bioanalytical Laboratory:	Celerion 621 Rose Street Lincoln, NE 68501

7 INTRODUCTION

Oxybutynin chloride is a well-known anticholinergic and antispasmodic agent that has gained widespread use in the pharmacological management of overactive bladder over the past 3 decades. It has shown efficacy, safety, and tolerability in the treatment of both adult and pediatric ***patients***. Oxybutynin is currently available for use in adults as immediate- and extended-release oral formulations, syrup, transdermal delivery systems (TDS), and as oxybutynin chloride gel (Gelnique®).

Oxybutynin chloride gel is formulated as a clear, colorless hydroalcoholic gel, available in a 1 gram unit dose that contains 100 mg oxybutynin chloride. This topical formulation was designed to provide the convenience of a once-a-day dosage form with decreased anticholinergic side effects compared to oral oxybutynin products and improved skin tolerability relative to the oxybutynin TDS (Oxytrol®).

Phase 1 investigations evaluating the pharmacokinetics and metabolism of ***oxybutynin chloride gel*** demonstrated that the gel provided sustained systemic delivery of therapeutic levels of oxybutynin.1 In a pharmacokinetic (***PK***) study in adults, application of 1 g of o***xybutynin chloride gel*** produced comparable oxybutynin absorption and plasma concentration profiles to 3.9 mg/day of Oxytrol transdermal administration.[1] The application of ***oxybutynin chloride gel*** to different anatomical sites (abdomen, thighs, and upper arms/shoulders) ***resulted in*** similar oxybutynin absorption from all of the sites.[2]

A Phase 3 study showed that ***oxybutynin chloride gel*** was effective in treating the symptoms of overactive bladder in adults and results from the same study indicated that the gel was safe and well tolerated, with improved skin tolerability over oxybutynin transdermal systems.[3]

Neurogenic bladder is a condition characterized by overactivity of both the detrusor and sphincter muscles resulting in incontinence, urinary retention, and bladder infections. The vast majority of neurogenic bladder dysfunction in the pediatric population is the result of a myelomeningocele.[4] When not treated adequately this condition will eventually impact the health of the kidneys.[4] Available data demonstrate that pediatric ***patients*** with detrusor overactivity associated with a neurological condition may benefit from improved bladder control with anticholinergic treatment.[5,6]

This Phase 4 study is being undertaken to provide information on the safety and efficacy of ***oxybutynin chloride gel*** in pediatric ***patients*** with neurogenic bladder dysfunction. In a previously conducted Phase 4 clinical study, children with neurogenic bladder were treated with oxybutynin TDS.[7] This study demonstrated that treatment with either 2.6 mg/day or 3.9 mg/day oxybutynin TDS improved the symptoms of detrusor overactivity and the urodynamic paratmers.[7] Oxybutynin and N-desethyloxybutynin (DEO) metabolite plasma concentrations in these pediatric ***patients*** did not differ significantly from those observed in adults administered Oxytrol (3.9 mg/day), suggesting comparable oxybutynin chloride bioavailability and metabolism in adults and children.[7] Therefore, the proposed doses of 0.5 g, 0.75 g, and 1 g ***oxybutynin chloride gel*** are in the range of oxybutynin TDS doses previously evaluated and shown to be safe and effective in this pediatric population.

The current standard of treatment is a combination of clean intermittent catheterization (CIC) and an anticholinergic agent, such as oxybutynin.[6] This combination has shown statistically significant and clinically meaningful changes from baseline in catheterization urine volume, as well as improvements in the percentage of catheterizations without leakage and in key urodynamic parameters.[8] These same clinical and urodynamic parameters will be used in the present study to evaluate the safety and efficacy of ***oxybutynin chloride gel*** when administered to pediatric ***patients***.

8 STUDY OBJECTIVES

8.1 Primary Objectives

The primary objectives of this study are:

- ***Pre-amendment 3***: To evaluate the efficacy ***of*** daily treatment ***with oxybutynin chloride gel compared to placebo*** in pediatric ***patients*** during the first 6 weeks of a 14-week treatment period.
- ***Post-amendment 3: To evaluate the efficacy of daily treatment with oxybutynin chloride gel in pediatric patients during the first 6-weeks of a 14-week open-label treatment period.***

8.2 Secondary Objectives

The secondary objectives of this study are to evaluate the pharmacokinetics, pharmacodynamics, safety, and ***skin tolerability*** of ***oxybutynin chloride gel*** in pediatric ***patients***.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This ***study was initiated as*** a double-blind, placebo-controlled study ***with an open-label extension, and is now amended to continuing to enroll patients under only open-label treatment***.

Pre-Amendment 3, patients ages 6 to >17 years, were randomly assigned 1:1 to receive double-blind oxybutynin chloride gel or placebo gel for 6 weeks, followed by an open-label, 8-week period to generate safety data. All patients began treatment with 0.75 g of gel/day for 2 weeks. Patients then returned to the clinic 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. Patients continued blinded treatment for 4 additional weeks until the end of the double-blind treatment period. Pre-Amendment 3, visits were identified numerically (ie, Visit 1 through Visit 8/Early Termination).

Post-Amendment 3, this study will continue as an open-label study for new patients enrolled under the present protocol (Amendment 3), with a similar patient population (ie, pediatric patients who have been diagnosed with detrusor overactivity that is associated with a neurogenic condition) and will also enroll younger patients (minimum age of 3 years).

For patients enrolled under Post-Amendment 3, this will be a multicenter, open-label, dose-titration study in pediatric patients, ages 3 years to ***< 17 years***, who have been diagnosed with detrusor overactivity that is associated with a neurogenic condition. ***Patients*** must be suitable candidates for anticholinergic therapy and must be using CIC for bladder control. ***No changes were made in the starting dose, compared to the Pre-Amendment 3 study design, in that all patients will begin treatment with 0.75 g of gel/day for 2 weeks. Patients 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. Patients will continue the adjusted dose for 12 additional weeks until the end of the open-label treatment period. Post-Amendment 3, visits will be identified alphabetically (ie, Visit A through Visit F/ET).***

In the Post-Amendment 3 study design (open-label treatment only), the study will consist of a screening period from Day -13 to Day -5 and a 14 week open-label treatment period. The total study duration for each patient will be approximately 16 weeks.

The screening period will include ***1*** clinic visit; Visit ***A*** (Screening Visit), where ***patients*** will be considered for inclusion in the study. Following Visit ***A***, all ***patients*** 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***). In addition, ***patients*** will be

asked to complete a 2-day urinary diary following the washout period and prior to Visit ***B***. To minimize ***time*** off treatment, ***patients*** may complete the washout period and urinary diary as close to Visit ***B*** as possible.

Patients who have completed the washout period and the 2-day urinary diary (***completed by the patient or parent/caregiver***) will have a baseline urodynamic evaluation performed at Visit ***B*** (Baseline Visit, Week 0 of treatment). ***Patients*** will be enrolled in the study following the urodynamic measurements. ***Patients*** will report back to the clinic for scheduled visits at Weeks ***2, 6, 10, and 14*** (± 2 days) as detailed ***below***.

Eligible ***patients*** will begin treatment ***the morning after Visit B (Week 0 of treatment)*** with 0.75 g of gel/day. This will be the start of the ***14***-week treatment period, and ***followed by*** 4 additional visits, on Weeks 2, ***6, 10,*** and ***14*** of treatment.

At Visit ***C*** (Week 2 of treatment), a blood sample will be collected for ***PK*** analysis. ***After study assessments at*** Visit ***C are completed***, the daily dose may be adjusted up to 1 g/day, down to 0.5 g/day, or remain the same at 0.75 g/day. 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. ***Patients*** will remain on this dose until the end of the ***treatment*** period.

A 2-day urinary ***diary*** will be completed prior to ***Visit D***, and urodynamic ***assessments*** will be performed ***at Visit D (Week 6 of treatment)***. A blood sample for ***PK*** analysis will ***also*** be collected ***at Visit D***.

Safety will be evaluated during the ***14***-week ***treatment*** period by monitoring adverse events ***(AEs)***, vital signs, ***and*** clinical laboratory evaluations, and ***by assessing*** skin erythema at the most recent application site.

Other evaluations will include a 12-lead electrocardiogram (ECG) at screening and an anticholinergic symptoms questionnaire at ***Visits C, D, E, and F.***

9.2 Rationale for Study Design and Control Group

Prior to Amendment 3, this study was designed as a double-blind, placebo-controlled study followed by an open-label safety extension, with a total planned enrollment of approximately 96 patients and the expectation that a minimum of 25 evaluable pediatric patients would complete the open-label extension period and provide long-term (14-week) safety data for oxybutynin chloride gel in pediatric patients.

Six weeks of treatment is sufficient [redacted] to observe a treatment effect. The additional 8 weeks of open-label treatment ***was intended to*** increase the number of patient exposures to oxybutynin chloride gel and generate long-term safety data. ***Post-Amendment 3 enrollment, the open-label treatment will allow for further ascertainment of efficacy and safety data for oxybutynin chloride gel in pediatric patients.***

[redacted]

[redacted]

The use of urinary diaries will generate ***data*** for assessment of primary and secondary endpoints in this study. ***Assessment of*** urodynamics is a ***customary*** and accepted method to measure changes in bladder function with oxybutynin and other anticholinergic agents.[9,10] The percent***age of*** catheterizations without leakage is a clinically meaningful endpoint, and catheterization volume ***is an accepted*** surrogate measure of changes in bladder capacity.

Safety monitoring for this study, including physical examination, vital signs, clinical laboratory measurements, and skin erythema assessments, are evaluations previously used to evaluate the safety of transdermal oxybutynin in pediatric ***patients. Post-Amendment 3, vision assessment prior to or at the Baseline Visit was added for patients < 8 years old and a vision symptom questionnaire for all patients was added to monitor visual changes.***

9.3 Selection of Study Population

The Pre-Amendment 3 include***d*** pediatric ***patients***, from ***ages*** 6 years to ***>17 years***, who ***had*** a diagnosis of detrusor overactivity associated with a neurological condition and ***were*** using CIC to control bladder function.

Post-Amendment 3 enrollment will include pediatric patients from ages 3 years to < 17 years, who have a diagnosis of detrusor overactivity associated with a neurological condition and are using CIC to control bladder function, with an enrollment of a minimum of 25 patients.

9.3.1 Inclusion Criteria

Patients will be considered for inclusion in the study if they meet all of the following criteria:

IN01. Are ***3*** years-of-age ***(6 years for Pre-Amendment 3)*** to ***< 17*** years-of age, at the time of screening

IN02. Have a diagnosis of detrusor overactivity associated with a neurological condition

IN03. Are using CIC

IN04. Are capable of completing the urinary diary with or without assistance from a parent or guardian

IN05. Have correctly completed the baseline urinary diary

IN06. Are capable of understanding and complying with the study requirements, are willing to provide assent to participate in the study as required by the institutional review board or ethics committee, and the parent(s) or legal guardian(s) have been adequately informed and have signed the informed consent/authorization to disclose PHI

IN07. ***For children < 8 years, have completed vision assessments within 12 months prior to the Screening Visit. If a child does not have a vision assessment performed within the last 12 months, it will be acceptable if it is performed by a trained healthcare professional (trained nurse, technician, or physician) at the study site or a separate site during the Screening or Baseline Visit (***Appendix 8***).***

9.3.2 Exclusion Criteria

Patient will be excluded from participation if they meet any of the following criteria:

EX01. Are pregnant or lactating

EX02. Have a patient-reported average CIC of more than 6 times per 24-hour period during the screening period, as captured by the 2-day urinary diary

EX03. Have 1 or more treatable conditions, other than neurogenic bladder dysfunction, that may cause urinary incontinence or urgency (eg, urinary tract infection or requirement for acute to intermittent use of diuretics)

Note: ***Patients*** with evidence of acute urinary tract infection may receive treatment and then be re-evaluated for entry into the study. Asymptomatic bacteriuria, which ***can be*** associated with CIC, is **not** an exclusionary condition.

EX04. Have any medical condition that precludes their safe participation in the study or may confound the outcome of the study (eg, history of lower urinary tract surgery within 6 months of screening, > 2 urinary tract infections within 6 months of screening, unstable diabetes mellitus; hydronephrosis unrelated to neurogenic bladder, or reflux Grade 4 or 5)

EX05. Have ECG with clinically significant abnormal results

EX06. Have had surgical bladder augmentation (eg, use of ileum or colon to provide surgical expansion of bladder capacity, gastrocystoplasty, detrusor myotomy) within 1 year of screening

EX07. Have any anatomical abnormalities of the urinary tract system that can affect bladder function

EX08. Have an active skin disorder, such as eczema, seborrhea, or psoriasis affecting the gel application areas

EX09. Have a known hypersensitivity or other contraindication to anticholinergic medications

EX10. Require treatment with medications that may interfere with the metabolism of oxybutynin, including antimycotic agents (eg, ketoconazole, itraconazole, miconazole), ***macrolide*** antibiotics (eg, erythromycin, clarithromycin), other anticholinergic agents (eg, oxybutynin, propantheline, ***dicyclomine, flavoxate, hyoscyamine***, tolterodine, darifenacin), ***or desmopressin (DDAVP)*** or require concomitant medications that may affect detrusor activity, including tricyclic antidepressants (eg, imipramine, doxepin, desipramine, nortriptyline, trimipramine, clomipramine, protriptyline)

Note: ***Patients*** who are taking excluded medications prior to starting the study can participate in the study only if the excluded medications can be safety discontinued at least 3 days before the initiation of the urinary diary. ***Patients*** who are taking solifenacin (***Vesicare®***) should discontinue treatment at least 11 days prior to the initiation of the urinary diary.

EX11. Have participated in another investigational drug study within 30 days prior to the Baseline Visit

EX12. ***Have been diagnosed with asymmetric/unequal or severe refractive error in either eye prior to the Baseline Visit. If a patient < 8 years old has known risk factors for eye disease before starting treatment (ie, family history of pediatric eye disease and/or symptoms of a vision disorder) it will be recommended, at the discretion of the investigator, that a comprehensive eye examination is performed by a pediatric ophthalmologist prior to enrollment.***

9.3.3 Patient Identification

Patient study identification numbers will be assigned at the Screening Visit. Patient numbers will be consecutive at each study site beginning with 001. Patient numbers will consist of the site number (3 digits) followed by the patient number (3 digits) at that site. Patient identification numbers will be used throughout the trial.

9.3.4 Removal of ***Patients*** from Treatment or Assessment

An attempt will be made to identify and follow every patient enrolled in the study through to completion. If a patient withdraws, or is withdrawn from the study by the investigator, the reason and circumstances for such early termination must be fully documented.

Patients may be withdrawn from treatment for the occurrence of a serious adverse event (***SAE***) or any other condition that may create a safety risk. ***The sponsor*** must be informed within 48 hours if any patient withdraws from the study regardless of cause. ***Patients*** who are withdrawn from the study may not be re-enrolled.

9.4 Study Treatments

9.4.1 Treatments Administered

Pre-Amendment 3, patients were randomized to receive oxybutynin chloride gel or placebo during the 6-week double-blind treatment period, and all patients received oxybutynin chloride gel during the 8-week open-label treatment period. Patients randomized to double- blind oxybutynin chloride gel started treatment at 0.75 g/day, and the dose may have been adjusted after 2 weeks of treatment to a higher or lower dose (0.5 g/day or 1 g/day) based on the investigator's clinical judgment and assessment of bladder symptoms and treatment side effects. All patients who entered the open-label safety period were started on 0.75 g/day oxybutynin chloride gel, and the dose may have been adjusted after 2 weeks of treatment as described for the double-blind treatment period.

Post-Amendment 3, no changes were made in the starting dose, compared to the Pre-Amendment 3 study design, in that all patients will begin treatment with 0.75 g of gel/day for 2 weeks. Patients 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. Patients will continue the adjusted dose for 12 additional weeks until the end of the open-label treatment period.

Patients or parents/***caregiver*** will apply the gel each morning to rotating application sites on the abdomen, upper arms/shoulders, and thighs. The person who applies the gel should wash ***his or her*** hands immediately after application with soap and water.

Patients should not bathe or shower sooner than 1 hour following a gel application. In the event of direct contact between unwashed or unclothed skin to which gel has been applied and the skin of another person, the contact area on the other person should be washed with soap and water as soon as possible.

9.4.2 Identity of Study Treatment

9.4.2.1 Description of ***Study Treatment***

Oxybutynin chloride gel is a pH 6.0 clear, colorless, hydroalcoholic gel containing 100 mg of oxybutynin hydrochloride salt per gram of gel. Each gram is designed to deliver approximately 4 mg oxybutynin to the systemic circulation. Inactive ingredients are alcohol, USP; glycerin, USP; hydroxypropyl cellulose, NF; sodium hydroxide, NF; and purified water, USP. The 0.5 g, 0.75 g, and 1 g doses are of identical composition and differ only in the amount of gel applied.

The study treatment is manufactured in accordance with current Good Manufacturing Practice ***and will be distributed to study centers by the sponsor***.

9.4.2.2 Packaging, Labeling, and Dispensing

The ***study treatment*** will be packaged in individual patient cartons containing a sufficient supply of sachets for the completion of ***the*** treatment period, plus an additional ***amount*** for supplies that are mishandled. ***Each patient carton*** will be color-coded by dose level ***(0.5, 0.75, or 1 g)***. The gel will be supplied as individually pouched 0.5 g, 0.75 g, and 1 g dose sachets of the active gel. Each sachet will be labeled with the ***protocol number, study treatment identification (ID), contents, caution*** statement (***Caution: New Drug – Limited by Federal Law to Investigational Use***) and ***the*** sponsor's name and address. These labeled sachets will be packaged in visit cartons to be dispensed to ***patients*** at their clinic visits. Two-part labels will be attached to each visit carton: one part will remain on the container and one will be detached when the container is dispensed to the study patient. ***The carton will be labeled with the protocol number, medication ID, contents, caution statement, the sponsor's name and address, and directions to apply contents of 1 sachet daily as directed. Immediately before dispensing the study treatment, the Investigator will write the patient's 6-digit identification number, patient's initials, and date dispensed on the label.*** The detachable portion will contain the dosing information for each patient (***ie, the starting dose of 0.75 g/day, or a later modified dose level of 0.5 or 1 g/day***). ***Dosing information*** will be ***recorded on*** the electronic case report form (***eCRF***).

9.4.2.3 Storage and Accountability

The study treatment will be stored in a secure location at controlled room temperature, 20°C ***to 25°C/68° to 77°F*** (with excursions allowed between 15°C ***and*** 30°C/***59°F and 86°F***) and away from direct sunlight.

The investigator shall maintain accurate study treatment inventory records, including the quantities and date of receipt of supplies from the sponsor, and the quantities and dates of dispensing to study participants. All ***study treatment*** supplies must be accounted for at study

termination and a written explanation provided for any discrepancies. All unused supplies shall be returned to the sponsor or, if authorized in writing by the sponsor, destroyed properly at the study site. Shipping and handling of all ***study treatment*** will conform to FDA regulations for investigational drug products.

Reasons for departure from the expected ***dispensing*** regimen will also be recorded. At completion of the study, to satisfy regulatory requirements regarding drug accountability, all ***study treatment supplies*** will be stored, inventoried, reconciled, and destroyed or returned to the sponsor according to applicable state and federal regulations. A written explanation must be provided for any discrepancies. The study monitor must review all records of investigational supplies prior to the return or destruction of any ***study treatment***.

9.4.3 Method of Assigning ***Patients*** to Treatment Groups

Pre-Amendment 3, patients were randomized to ***oxybutynin chloride gel*** or placebo treatment in a 1:1 ratio within each stratification level, ***using an*** interactive voice recognition system (IVRS). 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 ≤ 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.

Post-Amendment 3, no changes were made in the starting dose, compared to the Pre-Amendment 3 study design, in that all patients will begin treatment with 0.75 g of gel/day for 2 weeks. Patients 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. All patients will be assigned to oxybutynin chloride gel; patient enrollment will not be stratified.

9.4.4 Selection of Doses and Timing of Administration in the Study

Pre-Amendment 3, patients were randomized to receive oxybutynin chloride gel or placebo during the 6-week double-blind treatment period, and all patients received oxybutynin chloride gel during the 8-week open-label treatment period. Patients randomized to double-blind oxybutynin chloride gel started treatment at 0.75 g/day, and the dose may have been adjusted after 2 weeks of treatment to a higher or lower dose (0.5 g/day or 1 g/day) based on the investigator's clinical judgment and assessment of bladder symptoms and treatment side effects. All patients who entered the open-label safety period were started on 0.75 g/day oxybutynin chloride gel, and the dose may have been adjusted after 2 weeks of treatment as described for the double-blind treatment period.

Post-Amendment 3, no changes were made in the starting dose, compared to the Pre-Amendment 3 study design, in that all patients will begin treatment with 0.75 g of gel/day for 2 weeks. Patients 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. Patients will continue the adjusted dose for 12 additional weeks until the end of the open-label treatment period.

[redacted]

In a ***PK*** study in adults, application of 1 g of ***oxybutynin chloride gel*** produced comparable oxybutynin absorption and plasma concentration profiles to 3.9 mg/day of Oxytrol. In addition, a prior pediatric study with oxybutynin TDS at 1.3, 2.6, and 3.9 mg/day doses (Study O03010) demonstrated that the bioavailability and metabolism of oxybutynin in children was not significantly different than ***in*** adults.[7] [redacted]

9.4.5 Blinding

Pre-Amendment 3, the study involved double-blind treatment over the first 6 weeks, with subsequent open-label treatment. Blinding of this portion of the study will remain intact during Post-Amendment 3.

Post-Amendment 3, the study is entirely open-label.

9.4.6 Prior and Concomitant Therapy

Patients may not use concomitant medications that may affect detrusor activity, including anticholinergic agents (eg, oxybutynin, propantheline, dicyclomine, flavoxate, hyoscyamine, tolterodine, darifenacin), tricyclic antidepressants (eg, imipramine, doxepin, desipramine, nortriptyline, trimipramine, clomipramine, protriptyline), and desmopressin (DDAVP). The use of antimycotic agents (eg, ketoconazole, itraconazole, miconazole), and macrolide antibiotics (eg, erythromycin, clarithromycin) are also not allowed during the study.

Patients who are taking excluded medications prior to starting the study may participate in this study if they can safely discontinue the excluded medications at least 3 days before initiation of the urinary diary and remain off the medications for the duration of the study. ***Patients*** who are taking solifenacin (Vesicare®) should discontinue treatment at least 11 days prior to the initiation of the urinary diary and remain off this medication for the duration of the study.

All medications that the patient is taking at the time of study entry must be recorded on the concomitant medication form. In addition, any changes in concomitant medication or new medications added must be recorded in the eCRF. Document***ation will*** include the name of the drug, dose, frequency, route of administration, date of initiation and discontinuation, and the reason for administration.

9.4.7 Treatment Compliance

Compliance with the assigned study treatment regimen will be assessed by comparing the number of sachets expected to be used as based on the total number of treatment days with the actual number used (expressed as percentage of use/expected). ***Compliance*** will be ***assessed and recorded*** at each clinic visit and for the overall study.

9.5 Study Activities

The following sections (***Sections 9.5.1 to 9.5.4***) provide details of the study activities ***Post-Amendment 3 (ie, only open-label enrollment). Note that alterations from prior details are shown in bold italics and are further enumerated in the accompanying Summary of Changes document.*** A schedule of events table is presented in Section 15, Appendix 1.

9.5.1 Screening Period (***5 to 13 Days***)

The screening period will ***occur from Day -13 to Day -5*** and will include 1 clinic visit, Visit ***A*** (Screening Visit), where ***patients*** will be considered for inclusion in the study. Following Visit A, all patients taking anticholinergic medications will be asked to complete a 3-day minimum washout period (***11-day washout period if the patient was previously taking solifenacin***). Following the washout period, ***patients (or parents/caregivers)*** will complete a 2-day urinary diary on ***2*** consecutive days, ***prior to Visit B***. To minimize off-treatment time, ***patients*** may complete the washout period and urinary diary as close to Visit ***B*** as possible. All evaluations and procedures that will be conducted during the screening period are listed below in Section 9.5.1.1.

9.5.1.1 Visit ***A*** (Screening Visit)

Site personnel will perform the following:

1. Provide detailed explanation of the study.
2. Obtain informed consent and assent (if applicable)
3. ***Vision screening assessment. Prior to Baseline Visit patients who are < 8 years of age at the time of screening who have not had a vision examination in the last 12 months prior to screening are required to have a vision assessment prior to or at the baseline visit. The vision assessment can be performed at the study site or a separate site by a healthcare professional [nurse, technician, or physician] with the appropriate training.***
4. Assign 6 –digit identification number ***using IVRS***

The following evaluations must be completed before Visit ***B*** (Baseline Visit):

5. Review and document pertinent inclusion and exclusion criteria.
6. Record demographic information (sex, race, ethnicity, and date of birth).
7. Obtain medical history, including a history of the patient's incontinence.
8. Obtain ***prior and*** current medication use information.
9. Measure ***and record*** height and weight.
10. Measure ***and record*** vital signs (blood pressure, heart rate, respiratory rate, and temperature).
11. Record output of 12-lead electrocardiogram.

12. Conduct physical examination, which will include a review of the following: body as a whole; skin; head, ears, eyes, nose, throat (HEENT); cardiovascular; respiratory; musculoskeletal; neurologic; lymphatic/thyroid; and abdomen.
13. Collect blood and urine samples for laboratory evaluation, including urinalysis and urine culture (Appendix 2).
14. Collect urine sample for pregnancy test for all females of childbearing potential (Appendix 2).
15. Instruct ***patients*** to complete a 3-day minimum washout period, if ***patients*** are presently on anticholinergic or other excluded medication (***11-day washout period if the patient was previously taking solifenacin***).
16. Dispense 2-day urinary diary and review instructions for its completion (Appendix 3). Remind ***patients/caregivers*** that the urinary diary must be completed following the washout period, but prior to scheduled Visit ***B***. The patient/***caregiver*** should not be informed of the minimum diary requirements for eligibility.
17. ***Patients < 8 years old who have not had a vision examination in the last 12 months prior to screening will require a vision screening assessment prior to or at the Baseline Visit (Appendix 8). The vision assessment can be performed at the study site or a separate site by a healthcare professional (nurse, technician, or physician) with the appropriate training.***

9.5.2 ***Open-label*** Treatment Period (14 Weeks)

The ***14***-week, ***open-label*** treatment period will begin ***at*** Visit ***B*** (Baseline Visit, Week 0 of treatment). ***Patients*** should have completed the washout period and the 2-day urinary diary prior to Visit ***B***. If ***patients*** continue to meet eligibility criteria at Visit ***B***, a urodynamic evaluation will be conducted. All ***patients*** will apply 0.75 g of gel daily to rotating sites located on the abdomen, upper arms/shoulders, or thighs. If ***patients*** are not able to apply the ***study treatment***, their caregivers should perform this task on a daily basis.

9.5.2.1 Visit ***B*** (Baseline Visit) (Week 0 of Treatment)

Site personnel will perform the following activities ***at*** Visit ***B***:

1. Collect and review 2-day urinary diary and data.
   Patients who accurately complete the 2-day urinary diary but do not meet entry criteria based on number of catheterizations will not undergo further evaluation procedures. Patients who fail to accurately complete the urinary diary may be allowed to repeat the diary evaluation at the discretion of the investigator. ***Patients*** who then meet the criteria will be allowed to complete Visit ***B*** evaluation procedures. ***Patients*** failing to qualify for the study after the second diary attempt will be withdrawn from further study participation.
2. Update medical history and current medication use.
3. Review and document pertinent inclusion and exclusion criteria.
4. Measure vital signs (blood pressure, heart rate, respiratory rate and temperature).
5. Collect urine sample for urinalysis (use on site dipstick to determine presence of infection).
6. Perform urodynamic evaluations (Appendix 4).
7. Instruct patient/caregiver to complete the anticholinergic questionnaire (Appendix 5) ***and vision symptom questionnaire*** (Appendix 6).

8. Dispense ***study treatment*** kit (***dose of 0.75 g/day***), if the inclusion/exclusion criteria are met.
9. Instruct patient/caregiver on ***study treatment*** application (Appendix 7) and supervise application of first dose.
10. ***Patients < 8 years old who have not had a vision examination in the last 12 months prior to screening will be required to have a vision screening test prior to or at the Baseline Visit (***Appendix 8***). The vision assessment can be performed at the study site or a separate site by a healthcare professional (nurse, technician, or physician) with the appropriate training.***

9.5.2.2 Visit ***C*** (Week 2 of Treatment) Dose Titration Opportunity

Patients will return to the clinic after 2 weeks of treatment for evaluation and a dose titration opportunity. Site personnel will perform the following activities:

1. ***Perform study treatment*** accountability.
2. Record concomitant medication use.
3. Measure ***and record*** vital signs (blood pressure, heart rate, respiratory rate, and temperature).
4. Query for adverse events.
5. Assess erythema/application site adverse events at most recent application site ***and*** document findings.
6. Dose titration: Based on the investigator's clinical judgment and assessment of bladder symptoms and treatment side effects, the dose can remain the same ***at 0.75 g/day***, be increased to 1 g/***day***, or ***can be*** reduced to 0.5 g/***day***.
7. Collect blood sample for ***PK*** analysis and record the date and time of collection. Record ***date*** and time of last ***2 days*** gel applications (***visit date and day prior***).
8. Dispense ***study treatment*** kit for ***the next 4*** weeks of treatment and instruct patient/caregiver on ***study treatment*** application (Appendix 7).
9. ***Dispense 2-day urinary diary and remind patients that the urinary diary must be completed in the week prior to Visit D.***
10. ***Instruct patient/caregiver to complete the anticholinergic questionnaire (***Appendix 5***) and the vision symptom questionnaire (***Appendix 6***).***

9.5.2.3 Visit ***D*** (Week 6 of Treatment)

Site personnel will perform the following activities ***at*** Visit D:

1. ***Perform study treatment accountability.***
2. ***Collect and review 2-day urinary diary and data.***
3. ***Record concomitant medication use.***
4. ***Measure and record vital signs (blood pressure, heart rate, respiratory rate, and temperature).***
5. ***Query for adverse events.***
6. ***Assess erythema/application site adverse events at the most recent application site and document findings.***

7. ***Instruct patient/caregiver to complete the anticholinergic questionnaire (***Appendix 5***) and vision symptom questionnaire (***Appendix 6***).***
8. ***Perform urodynamic evaluations (***Appendix 4***).***
9. ***Dispense study treatment kit for the next 4 weeks of treatment.***
10. ***Collect urine sample for pregnancy test for all females of childbearing potential (***Appendix 2***).***
11. ***Collect blood sample for PK analysis and record the date and time of collection.***
12. ***Record date and time of last 2 days of gel applications (visit date and day prior).***

9.5.2.4 Visit ***E*** (Week 10 of Treatment)

Site personnel will perform the following activities at Visit E:

1. ***Perform study treatment accountability.***
2. ***Record concomitant medication use.***
3. ***Measure and record vital signs (blood pressure, heart rate, respiratory rate, and temperature).***
4. ***Query for adverse events.***
5. ***Assess erythema/application site adverse events at the most recent application site and document findings.***
6. ***Instruct patient/caregiver to complete the anticholinergic questionnaire (***Appendix 5***) and vision symptom questionnaire (***Appendix 6***).***
7. ***Dispense study treatment kit for the next 4 weeks of treatment.***

9.5.2.5 ***Visit F*** (Week 14 of Treatment) or Early Termination

Visit F will be the end of the open-label treatment period. Patients will undergo evaluation by site personnel who will perform the following activities:

1. Collect remaining study treatment and perform study treatment accountability.
2. Record concomitant medication use.
3. Measure ***and record*** vital signs (blood pressure, heart rate, respiratory rate, and temperature).
4. Query for adverse events.
5. Assess erythema/application site adverse events at the most recent application site ***and document findings***.
6. Instruct patient/caregiver to complete the anticholinergic questionnaire ***(***Appendix 5***) and the vision symptom questionnaire (***Appendix 6***)***.
7. ***Conduct physical examination, which will include a review of the following: body as a whole, skin, HEENT, cardiovascular, respiratory; musculoskeletal, neurologic, lymphatic/thyroid, and abdomen.***
8. ***Collect blood and urine samples for laboratory evaluation (***Appendix 2***).***
9. ***Collect urine sample for pregnancy test for all females of childbearing potential (***Appendix 2***).***
10. ***Collect blood sample for PK analysis and record the date and time of collection.***

9.5.3 Exit/Early Termination Visit

Study site personnel will ***make every*** attempt to follow the progress of every patient admitted to the study through to study completion. If a patient fails to return for a scheduled visit, a reasonable effort should be made to contact the patient and ascertain the reason(s) for not returning.

If a patient does not complete the study for any reason (including investigator discretion), the reason and circumstances for the patient's early termination must be fully documented. If possible, the assessments specified for the exit visit should be performed.

The ***sponsor*** must be informed within 48 hours if any patient withdraws from the study, regardless of the cause. ***Withdrawn*** patients may not be re-enrolled in the study and will not be replaced.

9.5.4 Early Termination Activities

Upon patient withdrawal/early discontinuation from the study, all evaluations scheduled at Visit ***F*** (Week ***14*** of treatment) should be completed at the termination visit. If the early termination visit occurs immediately after a visit in which a diary had been previously dispensed, the diary will be reviewed and collected.

9.6 Efficacy Assessment

The efficacy endpoints of the study will be evaluated based on information derived from the 2-day urinary diaries and urodynamic assessments recorded at baseline and during the treatment period.

9.6.1 Urinary Diary

The urinary diaries will be completed by each patient/caregiver during the week before ***Visit B and Visit D***. The 2-day urinary diary will be used to collect information for the parameters listed below. A sample urinary diary is ***provided*** in Appendix 3.

- Number of catheterizations per day
- Volume of urine collected at each (***after morning awakening***) catheterization
- Leakage incidents between catheterizations

9.6.2 Efficacy Variables

9.6.2.1 Primary Efficacy Variable

The primary efficacy ***endpoint 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***.

9.6.2.2 Secondary Efficacy Variables

Secondary endpoints include the CFB to Week 6 of treatment in the following (calculated from the 2-day urinary diary data):

- Average volume of urine collected per catheterization (***for Pre-Amendment 3 population only***);
- Average volume of urine collected ***at first*** (morning awakening) catheterization;
- Average number of catheterizations per day

9.6.2.3 Urodynamic Variables

Pharmacodynamics will be assessed for treatment under the Pre-Amendment 3 double-blind phase, treatment under the Post-Amendment 3 open-label phase, and both groups aggregated where appropriate. Pharmacodynamics will be based on urodynamic testing. The following ***parameters will be evaluated***:

- Maxim***al*** bladder capacity
- Detrusor pressures at maximum capacity
- Maximum amplitude of involuntary detrusor contractions
- Volume at first involuntary detrusor contraction
- Presence (versus total absence) of involuntary detrusor contractions at > 15 cm H2O

9.7 Safety Variables

Analyses and summaries will be performed for treatment under the Pre-Amendment 3 double-blind phase, the Pre-Amendment 3 open-label phase, and the Post-Amendment 3 open-label phase, with groups aggregated where appropriate.

Patients must be evaluated by a physician or an appropriately trained healthcare professional at every visit, and the evaluation must be documented. The procedures discussed below will be completed at the designated visits. Safety assessments should not be administered to the patient unless the patient is accompanied by his or her consented caregiver.

Safety evaluations will include the following:

- Adverse events
- Physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- Clinical laboratory evaluations including hematology, serum chemistries, and urinalysis
- Erythema at the gel application site

- Vision assessment in children < 8 years old prior to or at the Baseline Visit
- ***Visual assessment by investigator or designee (***Appendix 8***) and by using a visual symptom questionnaire (***Appendix 6***).***

9.7.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH-E2A).

For the purpose of the site's data collection responsibilities, any untoward event that was reported from the patient signed the informed consent form (ICF) until 30 days after the final protocol-defined study visit or, if the final visit does not occur, the last known dose of study treatment is to be considered an AE.

Examples of AEs are as follows:

- ***Changes in the general condition of the patient***
- ***Subjective symptoms offered by or elicited from the patient***
- ***Objective signs observed by the investigator or other study site personnel***
- ***All diseases that occur after signing informed consent, including any change in severity or frequency of pre-existing disease***
- ***All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study schedule***

Please note that medical procedures scheduled prior to consenting, but occurring during the study should not be captured as AEs, but should be listed in the medical history if related to a pre-existing condition.

9.7.1.1 Causality Assessment

For each AE, the investigator must provide an assessment of causal relationship to the study treatment. The causality assessment must be recorded on the eCRF. Causal relationship must be assessed by answering the following question:

Is there a reasonable possibility the study treatment caused the event?

Yes: There is evidence to suggest a causal relationship between the study treatment and AE, ie:

- ***There is a reasonable temporal relationship between the study treatment and the event, and/or***

- ***The event is unlikely to be attributed to underlying/concurrent disease, other study treatments, or other factors, and/or***
- ***Positive dechallenge and/or rechallenge exist***

No: There is no evidence to suggest a causal relationship between the study treatment and AE, ie:

- ***There is no reasonable temporal relationship between the study treatment and the event, or***
- ***The patient did not take the study treatment, or***
- ***The event is likely to be attributed to underlying/concurrent disease, other study treatments, or other factors, or***
- ***The event is commonly occurring in the (study) population independent of study treatment exposure***

9.7.1.2 Severity Assessment

The investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate page of the patient's eCRF. Severity, which is a description of the intensity of manifestation of the AE, is distinct from seriousness, which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality. Severity will be assessed according to the following scale:

Mild: ***A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.***

Moderate: ***A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.***

Severe: ***A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.***

9.7.1.3 Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- ***Results in death***
- ***Is life threatening***
- ***Requires inpatient hospitalization or prolongation of existing hospitalization***

- ***Results in persistent or significant disability/incapacity, or***
- ***Is a congenital anomaly/birth defect***

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of study treatment dependency or drug abuse.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes to determine whether they qualify as SAEs.

Preplanned hospitalizations (eg, elective procedures for pre-existing conditions that did not worsen, such as cosmetic surgery and hysterectomy) are excluded from SAE reporting.

9.7.1.4 Reporting Adverse Events and Serious Adverse Events

At each visit, patients are to be queried regarding any AEs or SAEs that have occurred since the previous visit. Patients will be asked to volunteer information with a nonleading question such as, "How do you feel since your last visit?" Study site personnel will record all pertinent information in the patient's eCRF.

All AEs must be recorded on the appropriate AE reporting page of the patient's eCRF whether or not they are considered causally related to the study treatment.

For every AE, the investigator must:

- ***Provide an assessment of the seriousness of the event (ie, is it an SAE?), as well as the severity and causal relationship***
- ***Document all actions taken with regard to the study treatment***
- ***Detail any other treatment measures taken for the AE***
- ***Document the outcome of the AE***

In addition, patients are to be reminded, as described in the ICF and in accordance with Section 9.7.1, to notify site personnel of any AEs occurring during the 30 day post-study period. Any AEs reported by the patient (or patient representative) during this period are to be recorded in original source documents. AEs are also to be recorded in the eCRF if at least one of the following conditions is met: 1) the event meets the criteria for an SAE (see Sections 9.7.1.3 and 9.7.1.5), and/or 2) the event is judged by the Investigator to be potentially causally related to study treatment.

Any AEs that are ongoing at the time of the final protocol-defined study visit will be followed until the condition returns to prestudy status, has resolved or stabilized, or can be explained as

being unrelated to the study treatment. If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the final protocol-defined study visit.

9.7.1.5 Immediate Reporting of Serious Adverse Events and Events of Special Interest

The Sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent is obtained.

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, the study site personnel must report the event to AbbVie Global Drug Safety on the SAE Form for Clinical Trials. The Sponsor's Study Physician may also be notified by telephone.

If, during follow-up, any nonserious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The site must transmit the SAE Form for Clinical Trials to the SAE fax number shown below. Even if an initial report is made by telephone, the SAE Form for Clinical Trials completed with all available details must still be faxed within 24 hours of knowledge of the event at the study site.

Supplemental information should be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the patient's eCRF. All SAEs are to be followed by the study staff until resolution or until the SAE is deemed stable. The Sponsor may contact the study site to solicit additional information or follow up on the event.

Fax the SAE Form for Clinical Trials to AbbVie Inc.

Global fax number for SAE or Pregnancy Reporting:
1-714-796-9504 (backup fax 1-714-246-5295)
or email it to IR-Clinical-SAE@abbvie.com.
In case of fax failure or the site does not receive confirmation of receipt of the fax, the site must email the report to IR-Clinical-SAE@abbvie.com.

Medical Emergency phone number: 1-800-503-8745

9.7.1.6 Reporting of Pregnancies Occurring During the Study

Study site personnel must report every pregnancy from the time the patient signs the ICF until 30 days after the last dose of study treatment. Within 24 hours of learning of the pregnancy, the study site personnel must report the event to Allergen Global Drug Safety on the Clinical Trial Pregnancy Form and fax it to the SAE/Pregnancy fax number stated in Section 9.7.1.5,

even if no AE has occurred. Pregnancies in female partners of male patients occurring during the time frame described above must also be reported.

The pregnancy must be followed to term and the outcome reported by completing a Clinical Trial Pregnancy Form. If the pregnancy is associated with an SAE (e.g., if the mother is hospitalized for hemorrhage), a separate SAE Form for Clinical Trials must be filed as described in Section 9.7.1.5 with the appropriate serious criterion (e.g., hospitalization) indicated in addition to the Pregnancy Form.

9.7.1.7 Potential Hy's Law Cases

Criteria for potential Hy's Law cases are as follows:

- ***Alanine Aminotransferase or Aspartate Aminotransferase ≥ 3x upper limit of the normal range (ULN) AND***
- ***Total Bilirubin ≥ 2xULN AND***
- ***Alkaline Phosphatase < 2xULN***

Study site personnel must report every patient who meets these potential criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time he or she signs the ICF for the trial until 30 days after the final protocol-defined study visit or the last known dose of study treatment (if the final visit does not occur).

A laboratory alert for potential Hy's laws cases will be in place and must notify investigators and the Sponsor immediately when the above criteria have been met. A potential Hy's law case must be faxed to the Sponsor on an AE of Special Interest Form as soon as possible (within 24 hours of learning of the potential Hy's law) to the SAE/Pregnancy fax number stated in Section 9.7.1.5, even if no AE has occurred. The eCRF for potential Hy's law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the medical monitor and in accordance with the FDA "Guidance for Industry: Drug Induced Liver Injury-Pre-Marketing Clinical Evaluation" July 2009.

Medical Emergencies and Emergency Protocol Deviations

In medical emergencies, the investigator will use medical judgment and remove the patient from immediate harm. The investigator will then immediately notify the sponsor and the IRB regarding the type of emergency and the course of action taken.

An investigator shall notify the ***sponsor's medical safety physician*** and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a patient in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for any changes in or deviations from the protocol. All deviations must be documented on the ***eCRF***.

The following contact will be used for all communications with the medical safety physician of this study:

Primary Contact: [redacted] ***M.D., PH.D.***
AbbVie Inc. [redacted]
1 North Waukegan Road, North Chicago, IL 60064
Off: [redacted] ***Fax:*** [redacted]
Mobile: [redacted]
Email: [redacted]

Medical emergency call center: 1-800-503-8745
Global fax for serious adverse events or pregnancy reports: 1-714-796-9504
(backup fax: 1-714-246-5295)
Email: IR-Clinical-SAE@abbvie.com

Sponsor Reporting Obligations

The sponsor will forward all reportable adverse events to the appropriate regulatory authorities and participating investigators according to 21 CFR 312 and any other applicable regulations.

9.7.2 Clinical Laboratory Evaluations

A blood and urine sample for clinical laboratory evaluations (serum chemistries, hematology, and urinalysis) will be collected from all ***patients*** at Visit 1 and at Visit 8 ***Pre-Amendment 3 and at Visit A and at Visit F Post-Amendment 3***. A sample for a urine culture will also be collected at Visit 1 ***(Pre-Amendment 3) or Visit A (Post-Amendment 3)***. A urine sample for dipstick urinalysis will be collected at Visit 2 ***(Pre-Amendment 3) or Visit B (Post-Amendment 3)*** to determine if there is any sign of bacterial infection. Urine samples for pregnancy testing will be collected from female patients of childbearing potential at Visits 1, 6, and 8 ***(Pre-Amendment 3) or Visits A, D and F (Post-Amendment 3)***.

Samples will be collected, processed, stored, and shipped according to the specific instruction for each test. A detailed list of laboratory evaluations is included in Appendix 2.

All out-of-range laboratory values that are considered by the investigator to be clinically significant and represent a change from baseline will be recorded as adverse events.

9.7.3 Application Site Erythema Assessment

Skin reactions at the most recently applied gel application site will be assessed for severity of erythema, at each clinic visit ***during the treatment period***. Other reactions such as itching, edema, papules, patient-reported erythema, etc. will be recorded as ***AEs*** using standard medical terminology. The following grading scale will be used to assess skin erythema:

0 = None:	no visible erythema
1 = Mild:	faint or barely perceptible pink color
2 = Moderate:	bright pink or sunburned appearance
3 = Severe:	beet-red appearance

Where there are multiple areas of erythema, the most severe rating should be recorded. Severe reactions (Grade 3) ***and*** clinically significant problems noted by the patient, investigator, or staff should be recorded as adverse events and will be followed through to resolution.

9.7.4 Physical Examination

A physical examination will be performed at Visits 1 and 8 ***(Pre-Amendment 3) or Visits A and F (Post-Amendment 3)***, and will include a review of the following: body as a whole, skin, HEENT, cardiovascular, respiratory, musculoskeletal, neurologic, lymphatic/thyroid, and abdomen. Height and weight measurements will be recorded at ***screening***.

9.7.5 Vital Signs

Vital signs will be measured at each visit and will include blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature.

9.8 Other Assessments

Other evaluations that will be performed during the study duration include determination of racemic and enantiomeric oxybutynin and N-desethyloxybutynin plasma concentrations and concomitant medication use.

9.8.1 Determination of R- and S- Oxybutynin and N-desethyloxybutynin Plasma Concentrations

Venous blood samples will be collected at Visits 3, 4, 5, and 6 ***(Pre-Amendment 3) or Visits C, D, and F/ET (Post-Amendment 3)*** for determination of oxybutynin and N-desethyloxybutynin plasma concentrations.

Blood samples (approximately 6 mL) will be collected into labeled purple top, EDTA collection tubes. They will be processed for plasma according to the standard procedure at the study site and the resulting plasma sample will be divided into ***2*** equal aliquots for storage at –20ºC. The samples will be sent to a contract laboratory for analysis of R- and S-oxybutynin and N-desethyloxybutynin concentrations by a validated bioanalytical method. [redacted]

9.8.2 Medical History

The patient's medical history will be taken ***at*** Visit***s*** 1 ***and 2 (Pre-Amendment 3) or Visits A and B (Post-Amendment 3)*** and will include an account of the underlying disease state and its management, including CIC and current medications use.

9.8.3 Electrocardiograms

A 12-lead ECG will be recorded at screening. The investigator will evaluate the ECG tracing for any clinically significant abnormalities.

9.8.4 Concomitant Medication Use

Patients will be queried at each clinic visit concerning the use of medications. Concurrent medications used by the ***patients*** will be documented, including the name of the drug, the dose, the frequency, the route of administration, the date of initiation and discontinuation, and the reason for the medication.

Guidelines for prohibited drugs listed in the inclusion/exclusion criteria (Section 9.3.2) are to be followed.

9.8.5 Anticholinergic Symptoms Questionnaire

Patients/caregivers will be asked to complete an anticholinergic symptoms questionnaire ***at*** Visits 2, 6, and 8 ***(Pre-Amendment 3) or Visits B, C, D, E, and F (Post-Amendment 3)***. The questionnaire will ask ***patients***/caregivers to describe the intensity of any side effects that may be associated with the administration of anticholinergic medications (Appendix 5). ***Adverse events associated with the administration of anticholinergic medications detected on the questionnaire will be reported on the Adverse Event Form. The severity of the event and the relationship to the study drug will be assessed by the investigator and reported on the Adverse Event Form.***

9.8.6 *Vision Symptom Questionnaire*

Post-Amendment 3, patients/caregivers will be asked to complete a Vision Symptom Questionnaire at Visits B, C, D, E, and F (Appendix 6). The questionnaire will ask patients/caregivers to describe any visual impairment or eye conditions for the patient.

Adverse events of vision disorders and/or symptoms detected on the Vision Symptom Questionnaire will be reported on the Adverse Event Form. The severity of the event and the relationship to the study drug will be assessed by the investigator and reported on the Adverse Event Form.

If a patient < 8 years old has started treatment and develops visual or ophthalmologic symptoms (ie, blurry vision, dry eye, dilated pupils, constant squinting, eyes drifting outward) it will be recommended that the patient is referred to a pediatric ophthalmologist for a comprehensive eye examination.

9.9 Appropriateness of Measurements

Urinary diaries are non-invasive tools that provide a record of bladder function in neurogenic and non-neurogenic conditions. The data collected from these diaries give an indication of urinary patterns and severity of symptoms. The urinary diary can be used effectively to assess improvement of urinary incontinence during treatment and is an appropriate tool to use in this study.

Urodynamic measurements are the gold standard for evaluating bladder and sphincter function and for documenting the effectiveness of new drugs and treatment paradigms. Urodynamic data can provide supporting evidence of changes in bladder function following treatment with anticholinergics.

The safety assessments, including adverse events review, physical examination, vital signs, and laboratory evaluations represent standard evaluations in clinical studies evaluating anticholinergic agents. The assessment of skin erythema at the local application site is useful in determining the irritation potential of transdermal applications, like the oxybutynin topical gel.

The sparse blood sampling methodology is appropriate for this pediatric study, to minimize the amount of blood sampling and for the determination of average oxybutynin and N-desethyloxybutynin plasma concentrations.

10 QUALITY CONTROL AND ASSURANCE

The sponsor will implement and maintain quality control procedures to ensure that this study is conducted, and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

The sponsor or designee will routinely conduct monitoring and/or auditing visits to the study centers to verify the adherence to the study protocol, the protection of the rights and well- being of the ***patients***, and the accuracy and completeness of reported study data recorded on the source documentation.

11 PLANNED STATISTICAL METHODS

11.1 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 ***patients*** 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 ***patients*** to evaluate the safety and efficacy of ***oxybutynin chloride gel*** treatment in a pediatric population. ***Patients were*** randomized in a 1:1 fashion to ***oxybutynin chloride gel*** or placebo within each stratification level, which ***were*** based on age, weight, and gender. 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 ***patients*** per treatment group, and then 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 (patients enrolled Post-Amendment 3) will include a minimum of 25 pediatric patients aged 3 to < 17 years (efforts will be made to enroll a greater number of patients 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 patients with 14 weeks of exposure.

11.2 Analysis Populations and Databases

Statistical analysis and data tabulation will be performed using ***data from the open-label period for patients enrolled after Amendment 3 and the data from the double-blind and open-label periods for patients enrolled prior to Amendment 3 in*** the following patient populations unless specified otherwise:

- Safety populations:
  - ***Post-Amendment 3 open-label safety population***
  - ***Pre-Amendment 3 double-blind safety population***
  - ***Pre-Amendment 3 open-label safety population***
  - ***Combined open-label safety population (Pre- and Post-Amendment 3)***
- Intent-to-treat (ITT) populations:
  - ***Combined ITT population (Pre- and Post-Amendment 3; primary efficacy analysis population)***
  - ***Post-Amendment 3 ITT population***
  - ***Pre-Amendment 3 ITT population***

- Per-protocol (PP) populations:
  - ***Post-Amendment 3 PP population***
  - ***Pre-Amendment 3 PP population***
- PK populations:
  - ***Post-Amendment 3 PK population***
  - ***Pre-Amendment 3 PK population***
  - ***Combined PK population (Pre- and Post-Amendment 3)***

The ***Post-Amendment 3 open-label*** safety population is defined as all ***patients*** who receive at least ***1*** dose of ***study treatment in*** the open-label period ***after Amendment 3***.

The Pre-Amendment 3 double-blind safety population is defined as all patients who receive at least 1 dose of study treatment in the double-blind period before Amendment 3.

The Pre-Amendment 3 open-label safety population is defined as all patients who receive at least 1 dose of study treatment in the open-label period before Amendment 3.

The combined open-label safety population is defined as all patients who receive at least 1 dose of study treatment in the open-label period before or after Amendment 3.

The primary efficacy analysis populations will be the ***Post-Amendment 3*** ITT population ***and the Pre-Amendment 3 ITT population***.

The combined ITT population will include all patients who have a baseline value for the primary efficacy variable in the Post-Amendment 3 open-label period or all randomized patients who have a baseline value for the primary efficacy variable in the Pre-Amendment 3 double-blind period.

The Post-Amendment 3 ITT population will include all randomized patients who have a baseline value for the primary efficacy variable in the Post-Amendment 3 open-label period.

The ***Pre-Amendment 3*** ITT population will include all randomized patients who have a baseline value for the primary efficacy variable ***in the Pre-Amendment 3 double-blind period***.

The ***Pre-Amendment 3*** PP population will include all ***patients*** in the ***Pre-Amendment 3*** ITT population who complete the ***double-blind*** treatment period of the study and who are without significant protocol violations.

The Post-Amendment 3 PP population will include all patients 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.

The PK population will include all ***patients*** who have at least 1 sample draw for plasma concentrations. The PK population will only be used in the summary statistics and analyses of the ***PK*** data.

Additionally, ***2*** types of visits are defined for the purposes of analysis and summary:

- Observed cases (OC)
- Last observation carried forward (LOCF)

The OC visits are defined to be those assessment values observed at each scheduled visit. All applicable efficacy and safety variables will be summarized using the OC visits.

The LOCF visit is defined as the last data recorded for each efficacy variable. This visit will be ***designated as*** Week 6 (LOCF). ***The Week 6 (LOCF) visit will be defined for the Post-Amendment 3 open-label period and the Pre-Amendment 3 double-blind period*** and will only be used to summarize efficacy data. The LOCF visit provides missing value imputation for ***patients*** who do not complete the ***open-label treatment period (Post-Amendment 3) or the double-blind treatment period (Pre-Amendment 3)*** of the study and will include all ***patients*** in the ***corresponding*** ITT population.

11.3 Efficacy Parameters

The primary efficacy variable ***for the Post-Amendment 3 open-label period and the Pre-Amendment 3 double-blind period*** will be the percentage of catheterizations without a leaking accident (continuous variable).

The following are secondary continuous efficacy variables that will be calculated:

- Average volume of urine collected per catheterization (f***or Pre-Amendment 3 population only***)
- Average volume of urine collected ***at first*** (morning awakening) catheterization
- Average number of catheterizations per day

The primary efficacy endpoint ***for the Post-Amendment 3 open-label period and the Pre-Amendment 3 double-blind period*** is defined as the CFB to Week 6 (LOCF) in the percentage of catheterizations without a leaking accident. The secondary efficacy endpoints are defined as the CFB in the secondary efficacy variables at Week 6 (LOCF).

Baseline is Visit 2 for Pre-Amendment 3, and baseline is Visit B for Post-Amendment 3.

11.4 Descriptive Summaries of Efficacy Parameters

Absolute values and CFB values for all the continuous efficacy parameters will be summarized for all visits, including Week 6 (LOCF), by dose level (0.5, 0.75, and 1.0 ***g and overall***) for the ***Post-Amendment 3 ITT and PP populations and by treatment group (placebo and oxybutynin chloride gel) for the Pre-Amendment 3*** ITT and PP populations using descriptive statistics including mean, 25th percentile, median, 75th percentile, SD, SEM, minimum, maximum, and number of ***patients***. Additionally, the above descriptive summaries will be provided for each age group (***3 to < 6 years***, 6 ***to < 12*** years, 12 ***to < 17*** years), for each weight category within ***each*** age group (***≤ 18 kg and > 18 kg for the 3 to < 6 years-of-age group***, ≤ 25 kg and > 25 kg for the

6 to ***< 12*** years-of-age group, and ≤ 50 kg and > 50 kg for the 12 to ***< 17*** years-of age group), and for each ***sex***.

11.5 Statistical Analyses of Efficacy Parameters

All analyses will be conducted with SAS® v***9.3*** or higher using procedures appropriate for the particular analysis.

11.5.1 Statistical Analysis of the Primary Efficacy Endpoint

The primary efficacy ***parameter is the CFB to Week 6 (or LOCF) in the percentage of catheterizations without a leaking accident. The primary efficacy parameter*** will be analyzed using an analysis of covariance (ANCOVA) model with the baseline measure of the primary variable as the covariate and treatment group ***and study part (Pre-Amendment 3 and Post-Amendment 3) as factors***.

To assess the effect of the study design, the primary efficacy parameter will be analyzed using a random effects mixed model using the combined data from the Pre-Amendment 3 double-blind treatment period and the data from the Post-Amendment 3 open-label treatment period. The model will include the baseline measure and other baseline characteristics as covariates and treatment (Pre-Amendment 3 double-blind placebo, Pre-Amendment 3 double-blind oxybutynin chloride gel, Post-Amendment 3 open-label oxybutynin chloride gel) as factors and will account for the heterogeneity between parts of the study (Pre-Amendment 3 vs Post-Amendment 3) by using a random effect for study part. If the analyses indicate heterogeneity, 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. For the Post-Amendment 3 ITT population, the significance of the change from baseline on the primary efficacy measure will be assessed from a 2-sided, 1-sample t-test. For the Pre-Amendment 3 ITT population the primary efficacy parameter will be analyzed using an ANCOVA model with the baseline measure of the primary variable as the covariate and treatment group as factors.

11.5.2 Statistical Analysis of the Secondary Efficacy Endpoints

For the Post-Amendment 3 ITT population, the analyses of the secondary efficacy parameters will assess the CFB for each variable at Week 6 (LOCF). The significance of the change from baseline on the secondary efficacy measures will be assessed from 2-sided, 1-sample t-tests. For the Pre-Amendment 3 ITT population, secondary efficacy parameters will be analyzed using ANCOVA models with the baseline measure of the efficacy variable as the covariate and treatment ***group as factor***.

11.5.3 Additional Analyses

The primary and secondary efficacy ***endpoints*** will be analyzed ***at Week 6 LOCF) for each of the per-protocol populations. The analyses will be similar to those described for the primary and secondary efficacy endpoint analyses.***

The primary and secondary efficacy endpoints will be analyzed at each OC visit for e***ach of*** the ITT and per-protocol populations. ***The analyses will be similar to those described for the primary and secondary efficacy endpoint analyses.***

11.5.4 Subgroup Analyses

The primary and secondary efficacy data analyses will be analyzed separately for age groups, weight group, and ***sex*** group ***for each ITT population***, as appropriate. Additionally, analysis of other important subgroups may be provided as well.

11.6 Safety Analysis

Safety variables will be summarized for ***each*** safety population using descriptive statistics and frequency distributions as defined in the following sections. Summaries will be provided overall and for each age group, weight group, and ***sex*** group.

11.6.1 Adverse Events

Key results will be presented for each safety population as follows:

- ***Post-Amendment 3 open-label safety population: by oxybutynin chloride gel dose level and/or overall***
- ***Pre-Amendment 3 double-blind safety population: by treatment group and/or treatment and dose level, and/or overall***
- ***Pre-Amendment 3 open-label safety population: by treatment group in the lead-in double-blind period and overall***
- ***Combined open-label safety population: by oxybutynin chloride gel dose level and/or overall***

The incidence of treatment-emergent adverse events will be summarized for the safety populations ***as described above***. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Summaries of the following types will be provided:

- Overall summary of treatment-emergent adverse events
- Summary of treatment-emergent adverse events by MedDRA system organ class, MedDRA preferred term, ***study treatment*** relationship, and ***severity***
- Summary of serious treatment-emergent adverse events by MedDRA system organ class, MedDRA preferred term, ***study treatment*** relationship, and ***severity***
- Summary of treatment-emergent adverse events by MedDRA preferred term and ***study treatment*** relationship in descending order
- Summary of treatment-emergent adverse events by MedDRA system organ class, MedDRA preferred term, and ***study treatment*** relationship for events leading to premature discontinuation from the study

These summaries will present the number and percentage of ***patients*** reporting an adverse event for each classification level as well as the number of events reported. The denominators for calculating the percentages will be based on the number of ***patients*** in ***each*** safety population for each ***tabulated*** group.

All adverse events, ***SAEs***, deaths, ***SAEs*** considered to be related to treatment, and adverse events leading to premature discontinuation from the study will also be provided in data listings.

11.6.2 Extent of Exposure

Summaries for duration of exposure for ***each*** safety population will be provided by treatment group for the ***Pre-Amendment 3 double-blind*** period, and by exposure to ***oxybutynin chloride gel*** for ***each of*** the ***Pre-Amendment 3 and Post-Amendment 3 open-label*** periods ***and the Pre-Amendment 3 double-blind*** and ***open-label*** periods combined. Duration of exposure to study ***treatment*** will be summarized using descriptive statistics (mean, 25th percentile, median, 75th percentile, SD, SEM, minimum, maximum, and number of ***patients***). Duration of exposure will be calculated as the difference between the last dose date and the first dose date plus 1 day.

Additionally, these summaries will present the number and percentage of ***patients*** for each interval (1-week multiples) of total exposure. The denominators for calculating the percentages will be based on the number of ***patients*** with exposure.

11.6.3 Laboratory Evaluations and Abnormalities

Continuous clinical laboratory analytes will be summarized for ***each*** safety population by ***double-blind*** period treatment group, double-blind treatment/***oxybutynin chloride gel*** sequence, or ***oxybutynin chloride gel*** only, ***as applicable, and by*** analyte and visit using descriptive statistics (mean, 25th percentile, median, 75th percentile, SD, SEM, minimum, maximum, and number of ***patients***). Categorical laboratory analytes, classified as normal or abnormal, will be summarized for ***each*** safety population by DB treatment group ***or oxybutynin chloride gel only group as applicable, and*** analyte and visit using the number and percentage of ***patients*** in each category. The denominators for calculating the percentages will be based on the number of ***patients*** in each treatment group or ***oxybutynin chloride gel*** only group, ***as applicable***, with nonmissing assessments at a particular visit for ***each*** safety population.

Shifts to values outside of the normal range will be presented as described above by summarizing the number and percentage of ***patients*** with evaluable shifts. An evaluable shift is one where both the baseline value (screening value) and the ***Pre-Amendment 3*** Week 14 or ***Post-Amendment 3 Week 14 or*** ET values are recorded. The denominators for calculating the percentages will be based on the number of ***patients*** in each treatment group, ***double- blind treatment/ oxybutynin chloride gel sequence***, or ***oxybutynin chloride gel*** only, ***as applicable*** who have an evaluable shift for a particular analyte. Evaluable shifts to be presented are N→L, N→H, H→L, H→N, L→H, and L→N for continuous variables and normal→abnormal for categorical variables.

All clinical laboratory values, abnormal clinical laboratory values, and clinically significant laboratory values will also be provided in data listings.

11.6.4 Vital Signs

Vital sign measurements will be summarized for ***each*** safety population by treatment group, double-blind ***treatment/ oxybutynin chloride gel sequence***, or ***oxybutynin chloride gel*** only ***group, as applicable***, and visit using descriptive statistics (mean, 25th percentile, median, 75th percentile, SD, SEM, minimum, maximum, and number of ***patients***). In addition, descriptive statistics will be presented for change from baseline (baseline is defined as Week 0 ***[Visit 2 for Pre-Amendment 3 and Visit B for Post-Amendment 3]***) for systolic and diastolic blood pressures and heart rate.

11.6.5 Physical Examinations

Physical examination assessments will be summarized for ***each*** safety population by DB treatment group ***or oxybutynin chloride gel*** only ***group, as applicable,*** and visit. For each body system and assessment category, the number and percentage of ***patients*** will be presented. The denominators for calculating the percentages will be based on the number of ***patients*** evaluated for each body system.

11.6.6 Skin Assessments 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 3 double-blind*** and ***open-label*** periods combined, ***and the Post-Amendment 3 open-label period***. Additionally, skin assessments for erythema will be summarized over all visits for each of the above described summaries. Summaries will present the number and percentage of ***patients*** for each erythema category (none, mild, moderate, and severe). The denominators for calculating the percentages will be based on the number of ***patients*** with nonmissing assessments.

11.7 Other Assessments

11.7.1 Demographic and Other Pretreatment Characteristics

Patient demographic and physical characteristic data ***and*** medical history data will be summarized for each analysis population using descriptive statistics (mean, 25th percentile, median, 75th percentile, SD, SEM, minimum, maximum, and number of ***patients***) for continuous variables and frequency distributions (number and percentage of patients) for categorical variables. Patient demographic data ***Pre-Amendment 3*** will be summarized by ***double-blind*** period treatment group and overall for the ***double-blind*** period and by ***oxybutynin chloride gel*** only for the ***open-label*** period and ***double-blind*** and ***open-label*** periods combined. Medical history data will be summarized by ***double-blind*** period treatment group and overall for ***double-blind*** period and by ***oxybutynin chloride gel*** only for the ***open-label*** period and ***double-blind*** and ***open-label*** periods combined. ***Post-Amendment 3 patient demographic and medical history data will be summarized by oxybutynin chloride gel level and overall.***

11.7.2 Medications

Medication usage will be coded using World Health Organization Drug Dictionary Enhanced Anatomical/Therapeutic/Chemical classification. Summaries of medications will be presented for the safety population by anatomical and therapeutic category and preferred name.

Pre-Amendment 3, summaries for the d***ouble-blind*** period will be provided by treatment and overall, and summaries for the ***open-label*** period and the ***double-blind*** and ***open-label*** periods combined will be provided for the ***oxybutynin chloride gel*** only group. Prior medication use and concomitant (on or after the first day of treatment) medication use will be documented and summarized separately. If the end date of prior medication occurs after treatment starts, then the medication will be reported as both prior and concomitant in the summaries. ***Summaries for Post-Amendment 3 will be provided by oxybutynin chloride gel dose level and overall.***

11.7.3 Compliance

Compliance with the ***study treatment*** for each patient/visit will be calculated using the following formula:

$$\text{Compliance} = \left(\frac{\#\text{ of sachets dispensed} - \ \#\text{ returned}}{\#\text{ expected}}\right) * 100$$

The expected number of sachets to be used for each patient will be based on the total number of treatment days. Compliance will be summarized by visit and over all visits using descriptive statistics (mean, 25th percentile, median, 75th percentile, SD, SEM, minimum, maximum, and number of ***patients***) for the ***Pre-Amendment 3 double-blind*** safety population. Compliance will be summarized for the ***open-label*** periods by visit and over all visits using the same descriptive statistics.

11.7.4 Urodynamic Variables

Urodynamic variables will be summarized for the ***Pre-Amendment 3 double-blind and Post-Amendment 3*** safety populations. ***Results will be presented*** by treatment group and visit and by treatment group, dose level, and visit for the ***Pre-Amendment 3 double-blind*** period ***and by oxybutynin chloride gel only and visit for the post-Amendment 3 open-label period*** using descriptive statistics (mean, 25th percentile, median, 75th percentile, SD, SEM, minimum, maximum, and number of ***patients***) for continuous variables and frequency distributions (number and percentage of ***patients***) for categorical variables. Summaries will be provided overall and for each age group and ***sex***. In addition, descriptive statistics will be presented for change from baseline (baseline is defined as Week 0) for continuous urodynamic variables.

11.7.5 *Anticholinergic Symptoms Questionnaire*

Anticholinergic symptom questionn***aire 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 questionn***aire 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***. Summaries will be provided overall and for each age group and sex. Summaries will present the number and percentage of ***patients*** for each category. The denominators for calculating the percentages will be based on the number of ***patients*** with nonmissing values in each treatment group or ***oxybutynin chloride gel*** only group, ***or dose level*** and visit, ***as applicable***. Additionally, shifts from baseline (baseline is defined at Week 0) 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.

11.7.6 ***Vision Symptom Questionnaire***

Vision symptom questionnaire data will be summarized for the Post-Amendment 3 safety population by visit and by dose level for the open-label period.

11.7.7 R- and S-Oxybutynin and N-desethyloxybutynin Plasma Concentrations

Plasma concentration data for ***oxybutynin*** and DEO plasma concentrations for the R-isomer, S-isomer, and R+S as well as the ratio of DEO to ***oxybutynin*** will be summarized for the pharmacokinetic population by visit. Summaries will be provided overall and for each age group and sex.

Linear ***or nonlinear*** regression, ***as appropriate***, will be used to ***investigate the*** relationship between the CFB in the efficacy variables and plasma concentrations, age and plasma concentrations, weight and plasma concentrations, and ***body mass index*** and plasma concentrations for each visit.

12 DATA HANDLING AND RECORDKEEPING

Electronic case report forms (***e***CRFs) will be designed and supplied by the sponsor. The ***e***CRFs represent a record of the patient's experience in the study. The data recorded in the ***e***CRFs must be supported by original (or source) medical records, as appropriate. Data recorded directly on the ***e***CRFs (ie, no prior written or electronic record of data) will be considered source data.

Prior to enrolling a patient in the study, the investigator must review all laboratory reports used for screening procedures. Documentation of this review must exist in the source documents (ie, the investigator must sign/initial and date the laboratory reports, etc) to provide evidence of the review and to indicate the date on which the review took place. The investigator will keep a log of all ***patients*** who are screened and record the reason(s) for their exclusion. ***e***CRFs should be completed only for ***patients*** who receive ***study treatment***.

Completion and correction of ***e***CRFs will follow the instructions ***provided by the sponsor***. Completed eCRFs will be ***electronically*** signed and dated by the investigator.

12.1 Data Generation and Analysis

After the ***site personnel complete*** data entry, electronic error and logic checks will be conducted to identify missing, incorrect, and/or out-of-range values. Discrepancies will be ***resolved through the system***.

12.2 Access to Source Documentation

The investigator agrees that the sponsor or its designated agents, the IRB, and the FDA or foreign regulatory agencies will have reasonable access to study source documentation for purposes of audit and review both during and after completion of the study. These monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study; to verify the accuracy and completeness of eCRFs; to assure that all protocol requirements, applicable regulations, and investigator's obligations are being fulfilled; and to resolve any inconsistencies in the study records. All participating ***patients*** will be required to signify their approval to permit inspection of their medical records by representatives of the sponsor, the IRB, and the FDA and/or foreign regulatory agencies, as needed.

12.3 Retention of Data

In compliance with ICH guidelines, the investigator shall maintain adequate records for the study, including medical records, laboratory reports, consent forms, ***study treatment*** disposition records, safety reports, information regarding participants who discontinued, and other pertinent data. The investigator shall maintain these records for a period of at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the ***study treatment***. These records should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. The sponsor will inform the investigator/institution as to when these records no longer need to be retained.

13 OTHER INFORMATION

13.1 Financing and Insurance

Financing and insurance is addressed in a separate agreement.

13.2 Publication and Disclosure Policy

Publication and disclosure policy is addressed in a separate agreement.

13.3 Termination of the Study

If the study is terminated prematurely or suspended, all the appropriate IRB and regulatory authority (ies) will be promptly informed of the termination or suspension and will be provided the reason(s) for the termination or suspension. All obligations and responsibilities of the sponsor and the investigator under GCP, the US CFR, and the Declaration of Helsinki will remain in force if the study is terminated prematurely.

14 REFERENCE LIST

1. Caramelli KE, Staskin DR, Volinn W. Steady-state pharmacokinetics of an investigational oxybutynin topical gel in comparison with oxybutynin transdermal system. Poster presented at Annual Meeting of the American Urological Association. May 17-22, 2008, Orlando, FL.
2. Caramelli KE, Thomas H, Stanworth S, Hoel G. Steady-state bioavailability of oxybutynin topical gel at 3 different application sites. Poster presented at Annual Meeting of the American Society of Consultant Pharmacists. November 19-22, 2008. New Orleans, LA.
3. Staskin DR, Dmochowski PR, Sand PK, MacDiarmid SA, Caramelli KE, Thomas H, Hoel G. Efficacy and safety of oxybutynin chloride topical gel for overactive bladder: A randomized, double-blind, placebo-controlled, multicenter study. J Urol. 2009 Apr;181:1764-1772.
4. Bauer SB. Neurogenic bladder: etiology and assessment. Pediatr Nephrol. 2008;23:541-551.
5. Franco I, Horowitz M, Grady R. Adams RC, De Jong T, Lindert K, Albrecht D. Efficacy and safety of oxybutynin in children with detrusor hyperreflexia secondary to neurogenic bladder dysfunction. J Urol. 2005 Jan;173:221-225.
6. Aslan AR, Kogan B. Conservative management in neurogenic bladder dysfunction. Curr Opin Urol. 2002;12:473-447.
7. A Multi-Center, Open-Label, Active-Controlled, Dose-Titration Study Evaluating the Safety, Efficacy and Pharmacokinetics of Oxybutynin Transdermal Systems in the Treatment of Detrusor Overactivity Associated with a Neurological Condition in Pediatric Subjects, Followed by a 12-Week Open-Label Safety Extension Study. Watson Study O03010, 2008.
8. Verpoorten C, Buyse G. The neurogenic bladder: medical treatment. Pediatr Nephrol 2008;23:717-725.
9. Chou FH, Ho CH, Chir MB, Lisenmeyer TA. Normal ranges of variability for urodynamic studies of neurogenic bladders in spinal cord injury. J Spinal Cord Medicine 2006;29:26-31.
10. Haferkamp, A Steahler G. Gerner HJ, Dorsam J. Dosage escalation of intravesical oxybutynin in the treatment of neurogenic bladder patients. Spinal Cord 2000;38:250-254.

15 APPENDICES

Appendix 1 Schedule of Events

Appendix 2 Clinical Laboratory Evaluations

Appendix 3 Sample 2-Day Urinary Diary

Appendix 4 Urodynamic Evaluation

Appendix 5 Anticholinergic Symptoms Questionnaire

Appendix 6 Vision Symptom Questionnaire for Parent/Caregiver

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Appendix 1 Schedule of Events

Post-Amendment 3

	ScreeningPeriod	*Open-Label Treatment Period*				
	Visit A[1]	*Visit B*	*Visit C*	*Visit D*	*Visit E*	*Visit F/ET*
Evaluation:	*-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 inChildren < 8 years	*X*[2]					
ConcomitantMedication	*X*	*X*	*X*	*X*	*X*	*X*
DemographicInformation	*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 UrinaryDiary	*X*		*X*			
Collect 2-day UrinaryDiary		*X*		*X*		
Local ErythemaAssessment[5]			*X*	*X*	*X*	*X*
Adverse EventAssessment			*X*	*X*	*X*	*X*
Anticholinergic Questionnaire		*X*	*X*	*X*	*X*	*X*
Vision SymptomQuestionnaire		*X*	*X*	*X*	*X*	*X*
Collect PK Sample &Record Date/Time			*X*	*X*		*X*
Dose Titration (ifnecessary)			*X*			
Study TreatmentDispensing		*X*[6]	*X*[6]	*X*	*X*	
Study TreatmentCompliance			*X*	*X*	*X*	*X*

1 ***All patients 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 patients < 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.***

Appendix 2 Clinical Laboratory Evaluations

Hematology (performed on whole blood)

Hemoglobin	Mean cell volume
Hematocrit	While blood cell (WBC) & differential
Red blood cell (RBC) count	Platelet count

Chemistry (performed on serum)

Albumin	Glucose
Alanine aminotransferase (ALT)	Lactate dehydrogenase (LDH)
Aspartate aminotransferase (AST)	Total bilirubin
Blood urea nitrogen (BUN)	Total protein
Gamma glutamyl transferase (GGT)	Creatinine
Sodium	Chloride
Potassium	Bicarbonate
Calcium	Phosphorus

Urinalysis (performed on urine)

Ketones	Protein
Specific gravity	Glucose
Potential for hydrogen (pH)	Blood
Appearance	Leukocyte esterase
Bilirubin	Microscopic examination

Other Labs (performed on urine)

Urine culture[1]

Urine pregnancy test[2]

[1] ***At screening only.***

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

Appendix 3 Sample 2-Day Urinary Diary

Instruction to Study Coordinator:

1. Complete the **PATIENT Initials** and **PATIENT Number** at the top of each diary page **AND** on the cover page, prior to providing the diary to the study participant and/or caregiver.
2. Instruct the study participant and/or caregiver on how and when to complete the diaryand to return the completed diary at their next visit.

Instructions for Study Participant and/or Caregiver:

1. Complete the urinary diary for **2 days in a row** (Day 1 and Day 2) prior to your nextvisit.
2. **Begin each day of the diary with the first catheterization after waking for the day**and continue collecting required information until you/your child wake up the next morning.
3. Record the actual date for each day of the diary (day month year). For example:
   - If Day 1 is 03 Jan 2011, then Day 2 will begin with the first catheterization afterwaking on 04 Jan 2011.
4. Collect and record the actual volume of ***first (morning awakening)*** catheterization on Day 1 and Day 2.
   - Use the supplied collection container to collect and measure the urine from ***the first (morning awakening)*** catheterization.
   - Record the volume of urine collected with ***first (morning awakening)*** catheterization in cubic centimeters (cc) or milliliters (mL) in the **VOLUME** column of your diary.
5. Record the number of catheterizations during the day; note: the volume needs to be recorded only for the first (morning awakening) catheterization.
6. Check the **Yes** or **No** box in the **LEAKAGE** column of your diary, indicating if anyleakage occurred since the last catheterization.
7. Bring the completed diary with you to your next visit.

Instruction to Study Coordinator upon return of diary:

1. Review the diary entries with the study participant and/or caregiver at the start of the visit.
2. If additional information is added to the diary to clarify an entry based on your review, include this information and initial/date your entries.

↓ Turn to next page to begin completing diary ↓

PATIENT INITIALS ☐☐☐ PATIENT NUMBER ☐☐☐☐☐☐ DIARY DATE ☐☐/☐☐☐/☐☐☐☐
DD MMM YYYY

DAY 1

EVENT NUMBER	VOLUME Volume of urine collected with first (morning wakening) catheterization	LEAKAGE Did any leakage occur since the last catheterization?
Cath #1 (First catheterization after waking in the morning)	VOLUME _____ (cc/mL)	☐ NO ☐ YES
Cath #2		☐ NO ☐ YES
Cath #3		☐ NO ☐ YES
Cath #4		☐ NO ☐ YES
Cath #5		☐ NO ☐ YES
Cath #6		☐ NO ☐ YES
Cath #7		☐ NO ☐ YES
Cath #8		☐ NO ☐ YES
Cath #9		☐ NO ☐ YES

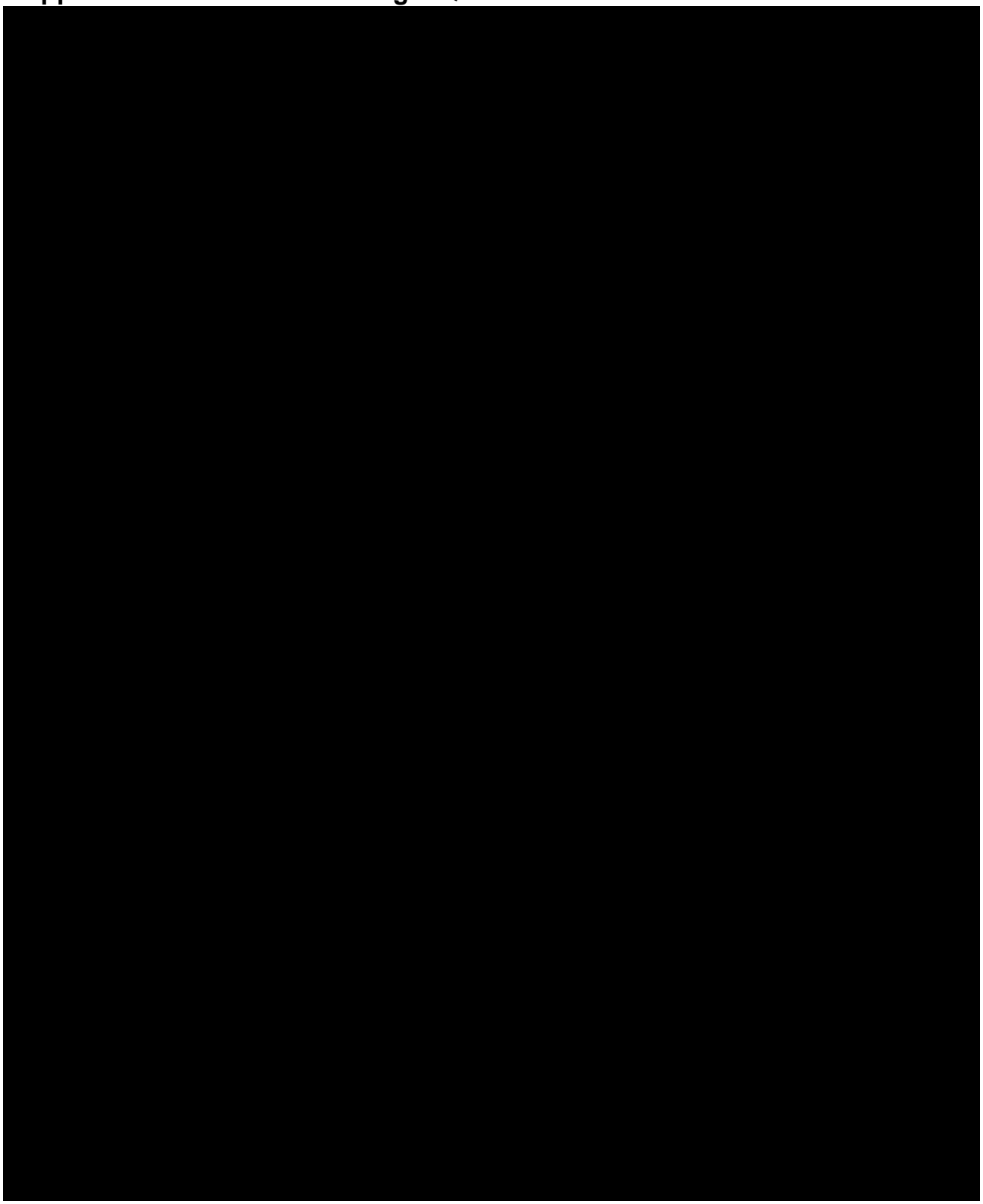
EVENT NUMBER	VOLUME Volume of urine collected with first (morning wakening) catheterization	LEAKAGE Did any leakage occur since the last catheterization?
Cath #10		☐ NO ☐ YES
Cath #11		☐ NO ☐ YES
Cath #12		☐ NO ☐ YES

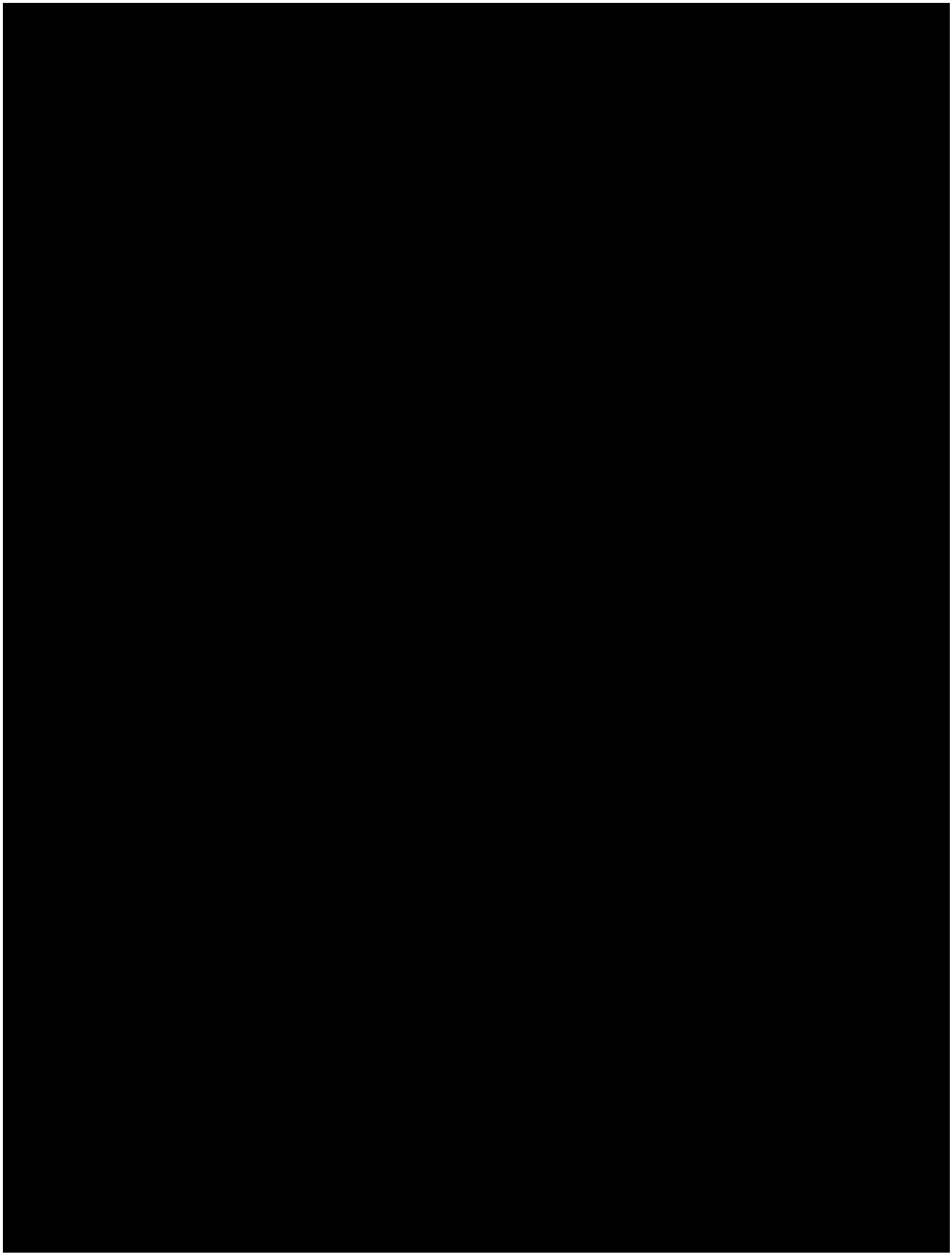
Appendix 4 Urodynamic Evaluation

The following procedures outline a standard clinical urodynamic evaluation. The Life-Tech Urovision system (or comparable system) with strip chart recording will be used for data collection. All equipment will be appropriately set up and regularly calibrated.

1. Patient will report to the urodynamic laboratory at the scheduled time.
2. Informed written consent and assent (if applicable) will be obtained from patient and parent/legal guardian.
3. After CIC the patient will assume the lithotomy position and will be prepped and draped in a sterile fashion.
4. All components of the urodynamic equipment will be checked for proper calibration and function.
5. The urethra will be lubricated, and anesthetized with lidocaine jelly, as needed.
6. The patient will be catheterized with a triple-lumen urodynamic catheter of a size appropriate for the pediatric patient (the smaller the better).
7. A small balloon catheter should be inserted into the rectum to measure intra-abdominal pressure.
8. The filling phase of the cystometrogram will be initiated by infusing water or saline through the side-hole channel at a rate of 10-25 mL/min in the supine or sitting position.
9. Pressure data from the bladder and rectal catheters will be recorded.
10. Captured urodynamic data will include:
    - Maximal bladder capacity
    - Detrusor pressure at maximum bladder capacity
    - Maximum amplitude of involuntary detrusor contractions
    - Volume at first involuntary detrusor contraction
    - Presence (versus total absence) of involuntary detrusor contractions at > 15 cm H2O.

Appendix 5 Anticholinergic Questionnaire





Appendix 6 Vision Symptom Questionnaire for Parent/Caregiver

Child Vision Symptom Questionnaire for Parent/Caregiver

Visit_____

Patient Initials:_____ **Patient #**_____

Place an "X" in the appropriate box as it applies to your child

Description	(circle Yes or No as indicated)	
Do you suspect anything is wrong with your child's eye/vision	Yes	No
Has your child ever been diagnosed with an eye condition	Yes	No
Have you observed any problems or change in the whites, pupils, lids, lashes or the area around the eyes	Yes	No
Has your child shown any signs ofabnormal sensitivity to light or dizziness	Yes	No
Has your child had any complaints of nausea or headaches	Yes	No
Turning of one eye (in, out, up or down)	Yes	No
Poking at the eyes or frequent rubbing	Yes	No
Excessive blinking	Yes	No
Unusual watering or discharge of the eye	Yes	No
Poor eye contact	Yes	No
Covering or closing an eye when looking at an item of interest	Yes	No
Abnormal head posture such as tilting the head to one side or moving forward or backward when viewing an item of interest	Yes	No
Squinting	Yes	No
Placing the head close to an item of interest	Yes	No
Inaccuracy in reaching for an item of interest	Yes	No

Source: Minnesota Department of Health (MDH); Community and Family Health Division; Child and Adolescent Health Unit; Vision Screening Procedures for Infancy, Childhood and School Age Children; June 2014. http://www.health.state.mn.us/divs/cfh/topic/visionscreening/content/document/pdf/vision_screening_manual.pdf.

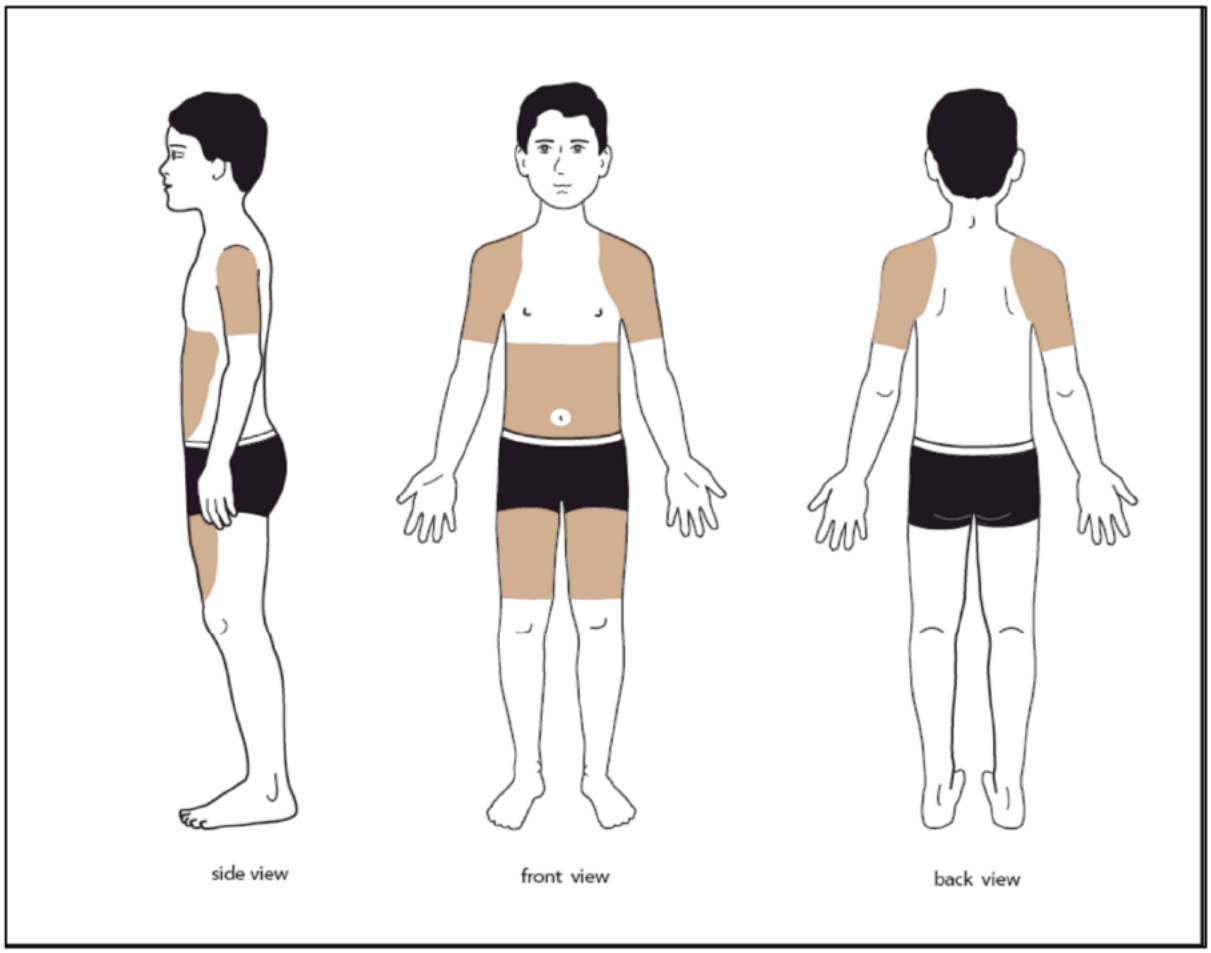
If a patient < 8 years old has started treatment and develops visual or ophthalmologic symptoms (ie, blurry vision, dry eye, dilated pupils, constant squinting, eyes drifting outward) it will be recommended that the patient is referred to a pediatric ophthalmologist for a comprehensive eye examination.

Appendix 7 Gel Application Instructions

The instructions below are for gel application by patient or caregiver:

- Bathing or showering should not occur sooner than 1 hour after gel application.
- If bathing before application, the area must be dried completely before gel application.
- Tear open the pouch at the indentation and express the complete contents either into your hand or directly on the abdomen, upper arm/shoulder, or thigh application area (see diagram on following page).
- Gently spread the gel on the application area in a continuous line covering as much of the application area as possible. It should be spread as uniformly and thinly as possible over the entire application area taking care not to transfer any material to any clothing. Care should also be taken not to apply gel to the area in or immediately around the naval during the abdominal applications.
- Gently work the gel into the skin over the entire application area until it dries. Do not continue rubbing after the gel had dried. Within 5 minutes after application, wash your hands thoroughly with soap and warm water.
- After application, the application site should be covered with clothing after the gel has dried (eg, a shirt or pants). In the event that unwashed or unclothed skin to which the gel has been applied comes in direct contact with the skin of another person within a day of application, the general area of contact on the other person should be washed with soap and water as soon as possible.

Gel Application Sites:



Appendix 8 Vision Assessment Instructions for Site

Visual acuity-LEA symbols

- ***Visual acuity is screened at a distance of 10 feet using the Lea symbols.***
- ***The child need not know these symbols, but must be able to match the indicated symbols on a wall chart with those on the response card.***

Equipment

- ***10' Lea Vision Chart Student Response Card Flashcards***
- ***Table and chair***
- ***Occluder with lip***

Facilities

- ***Room approximately 15 feet long or greater, well–lit and without glare.***

Procedure

Testing the right eye:

1. ***The child must be standing or sitting at a table with the response card in front, eyes at a 10-foot distance from the chart.***
2. ***The child must be conditioned to match symbols by pointing to the same symbol on the response card as is being shown with a flash card or pointed to on the chart.***
3. ***Begin screening with one person holding an occluder over the child's left eye.***
4. ***Another person points to the symbols on the Lea wall chart using caution not to cover the rectangle line with their finger or pointer.***
5. ***The child should point to the corresponding symbol on the response card.***
6. ***Start with the top line and continue downward showing one letter per line. If the child reaches the bottom line, show the remaining three symbols.***
7. ***If the child misses, go to the line above and show four different symbols in that line. If the child matches them correctly, proceed downward.***
8. ***To receive credit for a line, the child must correctly match each of the four different symbols on the line.***
9. ***The number recorded as the visual acuity is the smallest line the child can read correctly.***

Testing the left eye

- ***Cover the right eye and repeat the procedure***

Age five PASS
10/15 or better in each eye without a 2-line difference.

Re-screen/REFER
10/20 or worse in either eye or a 2-line difference in the pass range

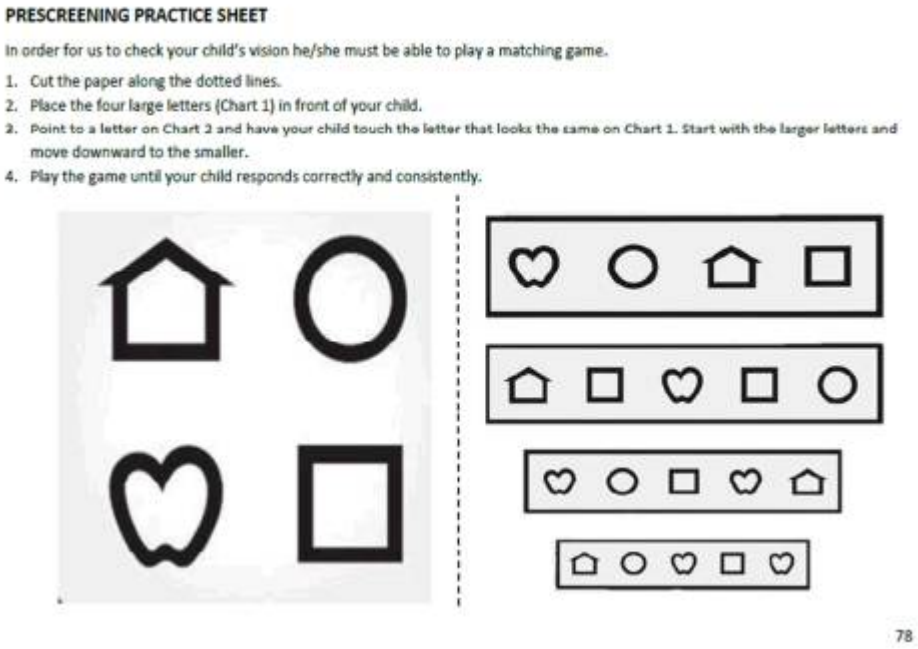
Age three to four PASS
10/20 or better in each eye without a 2-line difference

Re-screen/REFER
10/25 or worse in either eye or a 2-line difference in the pass range.

Considerations for screening special populations:

- ***The matching of the Lea symbols may be practiced before the screening***
- ***For some children with special needs it may be useful to reproduce the response card, cut and space them so that larger movements can be used when indicating the matching symbol.***

NOTE: At recheck, the poorer eye should be screened first. Children unable to perform the Lea chart should be given the procedures designed for younger children. Occluders should be cleaned between children.



PRESCREENING PRACTICE SHEET

In order for us to check your child's vision he/she must be able to play a matching game.

1. Cut the paper along the dotted lines.
2. Place the four large letters (Chart 1) in front of your child.
3. Point to a letter on Chart 2 and have your child touch the letter that looks the same on Chart 1. Start with the larger letters and move downward to the smaller.
4. Play the game until your child responds correctly and consistently.

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Reminders:

- ***The detection of vision disorders and symptoms during the study will be tracked by the adverse event reporting process. The severity of the event and the relationship to the study drug will be assessed by the investigator and reported on the Adverse Event Form.***
- ***Any patients with asymmetric/unequal or severe refractive error will be excluded from the study since aforementioned conditions can result in refractive amblyopia and may confound the study outcomes.***