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Study ID: 191622-121

Title: Long-term Extension Study of BOTOX® in the Treatment of Urinary Incontinence Due to Neurogenic Detrusor Overactivity in Patients 5 to 17 Years of Age

Protocol Amendment 2 Date: 14-Apr-2016

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STUDY TITLE

Long-term Extension Study of BOTOX® in the Treatment of Urinary Incontinence Due to Neurogenic Detrusor Overactivity in Patients 5 to 17 Years of Age

Protocol Number:	191622-121 Amendment 2
EudraCT Number:	2012-004898-30
Phase:	3
Name of Investigational Product:	BOTOX®
Sponsor:	Allergan (North America) 2525 Dupont Drive Irvine, California USA 92612 +1-714-246-4500 +1-800-347-4500 Allergan Ltd. 1st Floor, Marlow International, The Parkway, Marlow, Buckinghamshire SL7 1YL United Kingdom Tel: +44 (0) 1628 494444 Fax: +44 (0) 1628 494449
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[redacted]

Refer to the final page of this protocol for electronic signature and date of approval.

Approval Date: 14-Apr-2016

The following information can be found on FDA Form 1572 and/or study contacts page: Name and contact information of Allergan study personnel and emergency telephone numbers; name, address, and statement of qualifications of each investigator; name of each subinvestigator working under the supervision of the investigator; name and address of the research facilities to be used; name and address of each reviewing IRB; US 21 CFR 312.23 section 6(iii)b.

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.
- Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date

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Protocol Summary

Study Compound: BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex (US Adopted Name is OnabotulinumtoxinA)

Phase: 3

Study Objective: To evaluate the long-term safety and efficacy of BOTOX for the treatment of urinary incontinence due to neurogenic detrusor overactivity (NDO) in patients 5 to 17 years of age who have not been adequately managed with anticholinergic therapy.

Clinical Hypotheses: BOTOX (one or more treatment groups) has an acceptable long-term safety and efficacy profile when injected into the detrusor of patients 5 to 17 years of age with NDO.

Study Design

Structure: Multicenter, double-blind, long-term follow-up

Duration: Patients will participate in the study for at least 48 weeks following entry into the study and should have at least 12 weeks follow-up since the last treatment prior to exiting the study. The minimum duration is therefore 48 weeks, and the maximum duration is approximately 60 weeks (for patients who received their last treatment at week 48 with 12 weeks posttreatment follow-up).

Study Treatment Groups: There will be 3 dose options in this study: 50 U BOTOX (not to exceed 6 U/kg), 100 U BOTOX (not to exceed 6 U/kg), and 200 U BOTOX (not to exceed 6 U/kg). At each retreatment, the investigator can elect to keep the dose the same or increase the dose one level; if it is deemed that a dose reduction would be warranted then the patient should be exited from the study. (see Section 5.5 for further details). The dose decision will be based on the response to the previous treatment (for the first retreatment the reference treatment will be the initial treatment received in the preceding study). Both the preceding and subsequent dose will remain blinded until the interim analysis has been reported (see Section 7.7). The dosing options will depend on the investigator's decision as summarized below:

- Elect to keep the same dose as received at the previous treatment (dose not to exceed 6 U/kg)
- Elect to increase the dose compared to the previous treatment (dose not to exceed 6 U/kg):
    - if the patient received 50 U at the previous treatment, they would receive 100 U
    - if the patient received 100 U at the previous treatment, they would receive 200 U
    - if the patient received 200 U at the previous treatment, they would remain at 200 U

However, if the investigator requests a repeat dose escalation despite the patient having received 2 doses of 200 U, the patient will be exited prior to receiving any further treatments and will be followed-up for a minimum of 12 weeks since their last treatment. In addition, if the investigator assesses that the patient should not be retreated with the current dose and that a dose reduction would be warranted, the patient should be exited from the study as a reduction of dose in this study is not an option. In such cases, the patient will be followed up for a minimum of 12 weeks since their last treatment.

Controls: None

Dosage/Dose Regimen: Multiple treatments may be administered in this study. Request for retreatment can occur at scheduled clinic visits, scheduled telephone visits, or between scheduled visits. If the request is made at a scheduled clinic visit, then that visit will also become the qualification for retreatment visit, otherwise a qualification for retreatment clinic visit should be conducted within approximately 1 to 2 weeks of the patient/parent/caregiver request. (Note that those patients who qualified for retreatment in the preceding study 191622-120, at which point they exited, do not need to be requalified to receive their first retreatment in this study).

The qualification for retreatment criteria are:

- patient/parent/caregiver requests retreatment
- patient has a total of at least 2 daytime urinary incontinence episodes over the 2-day diary collection period
- at least 12 weeks has elapsed since their previous study treatment
- patient has not experienced a serious treatment-related adverse event at any time

Treatment will be administered within 4 weeks (28 days) after a patient qualifies for retreatment. Retreatment can be administered up to 48 weeks since enrollment on day 1.

All study treatments will be administered once all "day of treatment criteria" are fulfilled (see Section 5.9.1). Treatment will be administered via cystoscopy (rigid or flexible cystoscope) as 20 intradetrusor injections of 0.5 mL each evenly distributed, sparing the trigone. Administration will be under general anesthesia for all patients < 12 years of age. For patients 12 years and older, administration can be under local anesthesia (with or without sedation), or general anesthesia. Precautions for latex sensitivity or allergy will be taken, in accordance with local site practice.

Randomization/Stratification: No randomization or stratification will be performed in this long-term extension study.

[redacted]

Study Population Characteristics

Number of Patients or Subjects: It is estimated that approximately 100 patients will enter this extension study.

Condition/Disease: Urinary incontinence due to NDO

Key Inclusion Criteria:

- patient was aged ≥ 5 years to ≤ 17 years of age at the time of informed consent for the preceding study, 191622-120
- patient has participated in Study 191622-120 and fulfilled that study's exit criteria (completed the qualification for retreatment/exit visit or the week 48/exit visit if they never qualified for retreatment)
- patient is regularly using clean intermittent catheterization (CIC) to empty the bladder (CIC can be performed by either the patient or the parent/caregiver)

- [redacted]

[redacted]

Key Exclusion Criteria:

[redacted]

- patient has any newly diagnosed medical condition that may put them at increased risk with exposure to BOTOX, including newly diagnosed myasthenia gravis, Eaton-Lambert syndrome, or amyotrophic lateral sclerosis
- patient currently uses or plans to use a baclofen pump
- patient currently uses or plans to use an implantable or nonimplantable electrostimulation/neuromodulation device for the treatment of NDO
- patient currently uses or plans to use an indwelling catheter, rather than CIC, for treatment of NDO (NOTE: an indwelling catheter can be used if needed overnight as long as it is not used during the diary collection periods)
- [redacted]

[redacted]

Response Measures

Efficacy:

- daytime urinary incontinence episodes
- urine volume of first morning catheterization
- presence/absence of night time urinary incontinence
- time to patient request and time to qualification for retreatment

[redacted]

Health Outcomes:

- [redacted]
- Modified Treatment Benefit Scale (Modified TBS)

Safety:

- adverse events
- serious adverse events

General Statistical Methods and Types of Analyses:

One analysis population will be used in the statistical analysis of this study: the BOTOX-treated population. Data from the patients' participation in this extension study (191622-121) will be integrated with the corresponding patients' data from the preceding study (191622-120). Thus, the BOTOX-treated population will include all patients enrolled into the extension study who have received at least 1 BOTOX treatment over the course of the total evaluation period.

All efficacy and safety analyses will be based on the treatment actually received in each treatment cycle. Patients will be grouped to the nearest dose group (50, 100, or 200 U BOTOX) based on the dose actually received.

There will be no hypothesis testing in this long-term extension study. All data will be summarized with descriptive statistics and/or frequency tables.

For efficacy analysis, week 6 after each treatment will be the timepoint of main interest and the efficacy variable of key focus is change from baseline in the daily average frequency of daytime urinary incontinence episodes. Data will be presented by BOTOX treatment cycle according to the dose received at that treatment cycle (grouped to the nearest dose group, ie, 50, 100, or 200 U BOTOX), as well as by an overall BOTOX group (ie, regardless of dose). For each BOTOX treatment cycle, descriptive statistics will be provided for the daily average frequency of daytime urinary incontinence episodes at baseline and each posttreatment visit. The change from baseline (arithmetic mean and least-squares [LS] mean) and the 95% confidence intervals (CI) of the arithmetic and LS mean change will be provided.

Other efficacy analyses will include the proportions of patients achieving $\geq 50\%$, $\geq 75\%$, $\geq 90\%$, and 100% reduction from baseline in daytime urinary incontinence.

Duration of effect will be evaluated as time from study drug administration to request for retreatment, and dose-response analyses will include a nonparametric area under the curve (AUC) analysis of daily average frequency of daytime urinary incontinence episodes.

For other efficacy and health outcomes variables, descriptive statistics will be provided.

For safety variables, all safety analyses will be conducted on the BOTOX-treated population and data will be presented by BOTOX treatment cycle according to the dose received at that treatment cycle, with all patients allocated to the nearest dose group (50, 100, or 200 U BOTOX), as well as by an overall BOTOX group (ie, regardless of dose).

Sample Size Calculation:

For this extension study, no formal sample size calculation was used. Approximately 100 patients are anticipated to roll over into this study, which is assuming approximately 76% of patients randomized into Study 191622-120 will be available and willing to participate in this study.

[redacted]

[redacted]

[redacted]

1. Background and Clinical Rationale

Neurogenic Detrusor Overactivity in Pediatric Patients

The urinary bladder has 2 principal functions, to adequately store urine (storage phase), and to efficiently empty urine (voiding phase). Coordination of these functions is accomplished through a complex interaction between the peripheral innervations of the lower urinary tract and the micturition centers of the central nervous system.

Attainment of voluntary bladder control occurs once the appropriate coordinated neurological development has occurred, which usually starts from approximately 2 to 3 years of age. However, if there is a spinal cord lesion, an interruption of the spinal pathways and higher central nervous system micturition centers that control bladder function occurs. In children, this is most commonly due to incomplete neural tube closure during embryonic development with traumatic or neoplastic lesions of the spinal cord being less common. The most common form of incomplete neural tube closure is spina bifida whereby some vertebrae overlying the spinal cord are not fully formed and remain unfused and open. Myelomeningocele is the most commonly presenting form of spina bifida in which there is a protrusion of both the meninges that cover the spinal cord and the spinal cord itself through the unfused vertebrae; the meningeal membranes usually form a sac enclosing the spinal elements. In meningocele, an uncommon form of spina bifida, the vertebrae have developed more normally; however, the meninges have been forced into the gaps of the vertebrae. In the mildest form, spina bifida occulta, the gap in the vertebrae is so small that there is no protrusion of spinal cord or meninges and it often remains undetected. To avoid further nerve damage and infection in spina bifida patients, early surgical intervention usually occurs in order to put any protruding spinal cord and its nerve roots back inside the spine, which is then covered with meninges. This can lead to a subsequent complication during growth whereby the scar tissue at the site of the meningocele closure causes a tethering of the spinal cord.

A tethered cord can also occur through congenital malformations such as presence of a spur of bony tissue in the spinal canal (split cord syndrome), growth of fatty tissue at the base of the developing spinal cord that entangles it (lipomeningomyelocele), an incomplete involution of the distal spinal cord leading to a thickened filum terminale (tight filum terminale syndrome), or it may be due to an injury in later life. However, the common feature shared among tethered cord disorders is that the spinal cord is attached to the spinal column rather than hanging free in the canal. Since the spinal cord grows more slowly than

the spinal column, a tethered spinal cord becomes stretched and stressed over time, causing neurological damage in the cord.

Less commonly in the pediatric population, a spinal cord lesion can be caused by a direct spinal insult/injury, or due to a demyelination of the nerves (transverse myelitis); the latter may have various potential causes (eg, viral infection, immune disorder).

Regardless of the source of the spinal cord lesion, it commonly results in a neurogenic bladder, which often exhibits detrusor overactivity; since there is a known neurological cause this is termed neurogenic detrusor overactivity (NDO). Detrusor overactivity is defined as an involuntary detrusor contraction (IDC) during filling cystometry (Abrams et al, 2002), so this mainly affects the storage phase of the bladder. At bladder fill volumes which would normally be accommodated by the bladder, detrusor muscle contractions occur through efferent neuronal activity via the spinal micturition centers to the detrusor muscle. This abnormal efferent activity may be a consequence of the abnormal neuronal input to the detrusor as well as a malfunction of the afferent signals from the bladder. Essentially, the bladder has an inability to appropriately store urine resulting in uninhibited detrusor contractions that frequently result in uncontrolled urinary incontinence.

In addition to urinary incontinence, patients with NDO, frequently suffer from a low capacity bladder and high intravesical pressures with uncoordinated bladder sphincter activity (Van Gool et al, 2001). This can put at risk the upper urinary tract due to vesico-ureteric reflux, particularly when uncontrolled bladder contractions occur against a closed bladder outlet. This has been clearly demonstrated in pediatric patients (McGuire et al, 1981; Bauer et al, 1984; Gerridzen et al, 1992).

Currently Available Treatments for Neurogenic Detrusor Overactivity

Early intervention with clean intermittent catheterization (CIC) is the principal intervention for pediatric patients with NDO. The regular mechanical emptying of the bladder by CIC should not only reduce the degree of urinary incontinence, but also very importantly decrease the risk of upper urinary tract damage (Tekgül et al, 2012). CIC is recommended to be started as early as possible to make it easier for the procedure to be mastered and for children to accept it as they grow older (Joseph et al, 1989; Tekgül et al, 2012). Anticholinergic therapy is also commonly used in conjunction with CIC. The addition of anticholinergics may provide some additional relief; however their use can also be associated with problematic side effects. Other therapies are invasive, including surgically implanted neuromodulation devices, surgical augmentation of the bladder, and urinary diversion.

However, these approaches also have efficacy limitations and an inherent risk associated with the surgery so are frequently considered a last resort.

Mechanism of Action of BOTOX for Neurogenic Detrusor Overactivity

BOTOX inhibits synaptic vesicle-mediated neurotransmission through the cleavage of SNAP-25 (synaptosomal protein of molecular weight 25 kDa) in the nerve terminal. This is a protein component of the SNARE complex (soluble NSF [N-ethylmaleimide-sensitive factor] Attachment Protein Receptor) that is responsible for the successful docking and fusion of synaptic vesicles to the nerve terminal membrane. This process also provides a delivery mechanism for receptors such as TRPV1 (transient receptor potential vanilloid 1) to the nerve terminal as the receptors are embedded in the vesicle membrane and consequently exposed at the nerve terminal once the vesicle fuses with the nerve terminal membrane. BOTOX thus prevents both the release of neurotransmitters from within synaptic vesicles and the expression of certain receptors at the nerve terminal (Apostolidis et al, 2006).

There are several targets in the bladder that can be inhibited following injection of BOTOX into the bladder wall. A direct inhibition of detrusor contraction through inhibition of acetylcholine is a clear efferent pathway target (Coelho et al, 2010). In addition, modulation of various afferent pathways which also contribute to the condition have been proposed. BOTOX has been shown to inhibit various sensory neurotransmitters including substance P, calcitonin gene-related peptide, and adenosine triphosphate (Chancellor et al, 2008). It is also suggested from studies in humans that BOTOX may result in a reduction in certain sensory receptors that are thought to be upregulated in patients with detrusor overactivity, ie, TRPV1 and ionotropic purinergic receptor type 3 ($P2X_3$) receptors (Apostolidis et al, 2005; Apostolidis et al, 2006; Chancellor et al, 2008).

The inhibition of these various pathways through intradetrusor BOTOX injections therefore results in improvement in bladder function and patient symptoms.

BOTOX Development Program in Adult Neurogenic Detrusor Overactivity Patients

Allergan has completed a clinical development program for the use of BOTOX in adult patients with urinary incontinence due to NDO and it is licensed for use in many countries. Where registered, the licensed dose in adults is 200 U.

The adult development program and brief summary of results is provided below, however further details can be found in the BOTOX Investigator's Brochure.

The adult program was initiated with a phase 2 study (191622-511) that evaluated a single treatment of 200 and 300 U BOTOX versus placebo (N = 59). This study demonstrated clinically and statistically significant improvements with BOTOX compared to placebo in urinary incontinence and urodynamic parameters as well as an improvement in patient-reported health-related quality of life (HRQOL). Two pivotal phase 3 studies were subsequently conducted in spinal cord injury and multiple sclerosis patients who were not adequately managed with anticholinergic therapy (Study 191622-515, N = 416 and Study 191622-516, N = 275). Patients in both studies received 200 U BOTOX, 300 U BOTOX, or placebo administered as intradetrusor injections via cystoscopy. Patients could receive an additional treatment if prespecified retreatment criteria were fulfilled; patients received active treatment with BOTOX for this retreatment (200 or 300 U BOTOX). Patients were to remain in the studies for at least 48 weeks, and those receiving a second treatment were to be followed for at least 12 weeks post-treatment 2. In addition, patients could enter a long-term extension study (191622-094, 3 years duration) in which they could receive multiple treatments of BOTOX (initially of 200 or 300 U BOTOX but subsequently amended to only 200 U). At this time, the study is still ongoing; however data from an interim analysis are available.

Both pivotal phase 3 studies achieved the primary efficacy endpoint of significant reductions in urinary incontinence at week 6; reductions of approximately 20 episodes per week were observed in both BOTOX treatment groups compared to approximately 10 episodes per week in the placebo groups (Cruz et al, 2011; Ginsberg et al, 2012). Efficacy was further supported by achievement of the urodynamic secondary endpoints of a significant increase in maximum cystometric capacity (MCC) and a significant decrease in maximum detrusor pressure during the first involuntary detrusor contraction. Again, no clinically relevant difference was observed between the 200 and 300 U doses. The patient perception of benefit was reflected in the achievement of the HRQOL endpoint in both pivotal studies. The duration of effect of BOTOX was approximately 9 to 10 months.

With respect to safety, adverse events were primarily limited to local adverse events related to the urinary tract, in particular urinary retention and urinary tract infection (UTI). In patients not using CIC prior to treatment, a dose-dependent increase in post-void residual urine volume was observed post-treatment. A proportion of patients, both in the placebo and active dose groups, initiated CIC that was also dose-dependent.

A consistent efficacy and safety profile has been demonstrated with repeat treatment. The reductions from baseline in urinary incontinence episodes remained similar over repeated

BOTOX treatments as did the improvement in HRQOL. The most common adverse events remained urological eg, urinary tract infection and urinary retention, and the incidence of such adverse events did not increase with repeated BOTOX treatments.

Since there was no additional efficacy or benefit with the 300 U BOTOX dose compared to the 200 U BOTOX dose, and given that the 200 U BOTOX dose displayed a better safety profile, 200 U BOTOX was submitted for licensing registration, and approval has subsequently been granted in many countries at this dose.

Use of BOTOX in Pediatric Neurogenic Detrusor Overactivity Patients

Following the development of BOTOX for use in adults with urinary incontinence due to NDO, the efficacy and safety in the pediatric NDO population is being evaluated in Study 191622-120. This current study, 191622-121, is an extension of the initial pediatric study to enable an evaluation of long-term data over repeated treatments. The doses of BOTOX available for use in this extension study remain the same as those in the preceding study (ie, 50, 100, and 200 U with no dose to exceed 6 U/kg). However, in this extension study, at each retreatment the investigator has the option to change the dose of the patient's next BOTOX treatment based on the patient's response to their previous treatment. In addition, following further discussion with the US FDA, it was agreed that the minimum age requirement could be decreased from 8 years old to 5 years old at entry into the main study, 191622-120. Since NDO due to spina bifida is a congenital disease with lifelong consequences, the primary goal of treatment is early intervention in order to prevent worsening bladder pressures and preserve renal function, thereby halting the progression of kidney disease.

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

The objectives of this study are to evaluate the long-term safety and efficacy of BOTOX for the treatment of urinary incontinence due to NDO in patients 5 to 17 years of age who have not been adequately managed with anticholinergic therapy.

2.2 Clinical Hypotheses

BOTOX (one or more of the treatment groups) has an acceptable long-term safety and efficacy profile when injected into the detrusor of patients 5 to 17 years of age with NDO.

3. Study Design

This is a multicenter, double-blind, long-term extension study to the preceding study, 191622-120. Patients will roll over directly from the preceding study; the exit visit of study 191622-120 is also the entry visit (day 1) for Study 191622-121 (patients exit Study 191622-120 once they have qualified for retreatment, or at week 48 if they never qualified).

Patients can receive multiple double-blind treatments of 50, 100, or 200 U BOTOX (not to exceed 6 U/kg) in the extension study once they qualify for retreatment (for the first retreatment this qualification may have occurred in the preceding study). The dose received at any given treatment will be determined by the investigator based on the response to the preceding blinded treatment. The investigator can elect to keep the dose the same or increase the dose compared to the preceding treatment (if it is deemed a decrease in dose is warranted, the patient would be exited from the study). The actual dose received remains blinded (unless the patient is requested to exit the study via the IVRS, as described at the end of Section 5.5, or until the interim analysis has been reported as described in Section 7.7). The study medication will be administered via cystoscopy as 20 evenly spaced intradetrusor injections of 0.5 mL each, sparing the trigone.

Following any treatment, patients will have posttreatment follow-up clinic visits at weeks 2, 6, and 12, and then alternating telephone and clinic visits every 6 weeks thereafter until they qualify for further retreatment or exit the study. Request for retreatment can occur at any scheduled clinic or telephone visit, or between scheduled visits. If a request occurs at a scheduled clinic visit, this then becomes a qualification for retreatment visit, otherwise a qualification for retreatment clinic visit should occur within approximately 1 to 2 weeks of request. Patients exit the study once 48 weeks have elapsed since entry on day 1 and at least 12 weeks follow-up since their last study treatment has occurred (exit will therefore be between 48 and 60 weeks since study entry on day 1; the latter being for patients who received retreatment at week 48).

The efficacy measure of key interest is daytime urinary incontinence episodes, and the key timepoint is week 6 after each treatment.

3.1 Data Review Committee

An independent Data Review Committee (DRC) will be used for this study to review safety data. It will be composed of at least a study-independent non-Allergan physician and a study-independent Allergan statistician. Additional members may be included and ad hoc

members may also be invited depending on the safety findings and required scope of expertise.

Details regarding the DRC are included in the DRC charter, including committee membership, data review procedures, frequency of review, and communication between the DRC and others.

4. Study Population and Entry Criteria

4.1 Number of Patients

Approximately 100 patients are anticipated to roll over into this study, which assumes that approximately 76% of patients randomized into Study 191622-120 will be available and willing to participate in this study.

4.2 Study Population Characteristics

This study will include patients who, at the time of consent in the preceding study (191622-120), were 5 to 17 years of age, have urinary incontinence due to NDO, and had not been adequately managed with anticholinergics.

4.3 Inclusion Criteria

The following are requirements for entry into the study:

1. patient was aged ≥ 5 years to ≤ 17 years of age at the time of informed consent for the preceding study, 191622-120
2. patient has participated in Study 191622-120 and fulfilled that study's exit criteria (completed the qualification for retreatment/exit visit or the week 48/exit visit if they never qualified for retreatment)

[redacted]

5. patient must be regularly using CIC to empty the bladder (CIC can be performed by either the patient or the parent/caregiver)

[redacted]

4.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

[redacted]

5. patient has any newly diagnosed medical condition that may put them at increased risk with exposure to BOTOX including myasthenia gravis, Eaton-Lambert syndrome, or amyotrophic lateral sclerosis
6. patient currently uses or plans to use a baclofen pump
7. patient currently uses or plans to use an implantable or nonimplantable electrostimulation/neuromodulation device for the treatment of NDO
8. patient currently uses or plans to use an indwelling catheter, rather than CIC, for treatment of NDO (NOTE: an indwelling catheter can be used if needed overnight as long as it is not used during the diary collection periods)

[redacted]

[redacted]

11. patient has had previous botulinum toxin therapy of any serotype for any urological condition (other than the study medication) or for any nonurological condition since entry into the preceding study, 191622-120

[redacted]

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. Patients should be instructed to maintain a stable dose during the study, whenever possible. All medications and adjunct therapies should be recorded on the appropriate electronic case report form (eCRF). If the permissibility of a specific medication/treatment is in question, please contact Allergan.

For those patients who were taking anticholinergics at entry into the preceding study, 191622-120, they can continue to be taken during this study. In addition, the dose can be modified or their use discontinued; the reason for dose modification or discontinuation should be documented by the investigator. However, intravesical anticholinergics are prohibited throughout the study, as is the initiation of anticholinergic therapy.

Refer to Section 5.9.3 for information on permitted study treatment anesthesia.

4.5.1.1 Definition of Females of Childbearing Potential and Acceptable Contraceptive Methods

For females of childbearing potential (ie, females who are postmenarche), the following methods of contraception, if properly used, are generally considered reliable: oral contraceptives, patch contraceptives, injection contraceptives, implantable contraceptives, male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation), vasectomized partner, or sexual abstinence (when this is the lifestyle of the patient).

If a postmenarche female patient is sexually active, the investigator and each patient (and her parent/legally authorized representative, in accordance with local laws and IRB/IEC requirements) will determine the appropriate method of contraception to be used during the study.

If a female becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed and the patient will be exited from the study after appropriate safety follow-up, which should be at least 12 weeks since study treatment. The investigator will: (1) notify the patient's physician that the patient has been treated with BOTOX, and (2) follow the progress of the pregnancy. The investigator should document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

4.5.2 Prohibited Medications/Treatments

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, Allergan should be notified before the prohibited medication/treatment is administered.

The use of intravesical anticholinergic therapy is prohibited throughout the study. The initiation of anticholinergic therapy is also prohibited during the study (eg, those patients who were not using anticholinergic therapy during the preceding study, 191622-120, are not permitted to start anticholinergic therapy in this study). The use of other medications or therapies, other than anticholinergics, to treat the symptoms of NDO is also prohibited during the study.

Botulinum toxin treatment of any serotype other than study drug is prohibited for any indication. Immunization to any botulinum toxin serotype is also prohibited during the study.

Administration of intravesical capsaicin or resiniferatoxin is prohibited during the study.

Use of electrical stimulation and neuromodulation devices (implanted and external) for the treatment of overactive bladder (OAB) are prohibited during study participation (if a patient is enrolled into the study with a device still implanted, it must be inactive for the duration of the study).

Use of baclofen pumps are prohibited during the study.

Use of aminoglycoside antibiotic therapy is not permitted during study treatment administration. If a patient requires aminoglycoside antibiotic therapy during the trial, any study treatment administration must be delayed until the aminoglycoside antibiotic therapy is completed. Use of aminoglycoside antibiotics should also be avoided for 8 weeks after study treatment. Examples of such medications are: amikacin sulfate, gentamicin sulfate, kanamycin, tobramycin, netilimicin sulfate, streptomycin.

Anticoagulant medications (eg, warfarin and other coumadin derivatives), antiplatelet medications (eg, clopidogrel and aspirin [including low dose]) and any other medications with anticoagulative effects (eg, nonsteroidal anti-inflammatory drugs) are prohibited for a minimum of 3 days (or longer according to the clinical judgment of the investigator) prior to any study treatment, and must not be recommenced until the day following treatment(s).

Neuromuscular blocking agents may not be administered at the same time as the study treatment.

Indwelling catheters cannot be used to replace CIC and are prohibited during the study, except if needed overnight. However, an indwelling catheter cannot be used during the diary collection periods.

5. Study Treatments

5.1 Study Treatments and Formulations

BOTOX

Each vial of BOTOX (Botulinum Toxin Type A) purified neurotoxin complex, [redacted] (US Adopted Name is OnabotulinumtoxinA), contains: 100 units (U) of *Clostridium botulinum* toxin Type A, 0.5 mg albumin (human), and 0.9 mg sodium chloride in a sterile, vacuum-dried form without a preservative. One unit corresponds to the calculated median lethal intraperitoneal dose (LD_{50}) in mice. The study medication will be reconstituted with 0.9% sodium chloride (preservative-free).

5.2 Control Treatment

There is no control treatment in this study.

5.3 Methods for Blinding

Both patients and investigators will remain blinded to BOTOX dosage (unless the patient is requested to exit the study via the IVRS, as described at the end of Section 5.5, or until the interim analysis has been reported as described in Section 7.7).

The study medication will be packaged and labeled in identically appearing vials and reconstituted by an independent drug reconstitutor (IDR). The study medication will be identified as an investigational compound and the carton will also be labeled with the study number and kit number.

5.4 Treatment Allocation Ratio and Stratification

Treatment allocation will be as described in Section 5.5 with no stratification.

5.5 Method for Assignment to Treatment Groups/Randomization

There will be no randomization in this long-term extension study.

All patients who receive treatment in this study will receive BOTOX. The blinded dose received (50, 100, or 200 U BOTOX, not exceeding 6 U/kg) will be dependent on the assessment of the clinical response (efficacy and safety) to the previous blinded study treatment (which will have been 50, 100, or 200 U BOTOX, not exceeding 6 U/kg). The patient/parent/caregiver will be questioned on their treatment response to establish if, in their opinion, the current treatment response is adequate or if there was little or no treatment benefit and whether they would be willing/want to have a higher dose. They will also be questioned on whether the patient is experiencing side effects. Using this information, the investigator will use his/her own clinical assessment of the patient and apply the following criteria for the retreatment dose request:

- if the benefit/risk balance is evaluated by the investigator to be appropriate at the current dose, then the same dose would be requested
- if the investigator assessed that, although the preceding dose was well tolerated, the response received was insufficient and warrants a higher dose, then a dose increase would be requested

- if the investigator assessed that there were side effects that would warrant a lower dose, the patient would be exited from the study

Compared to the previous treatment, the investigator therefore has the following options:

- elect to keep the same dose as received at the previous treatment (not to exceed 6 U/kg)
- elect to increase the dose compared to the previous treatment (not to exceed 6 U/kg):
  - if the patient received 50 U BOTOX at the previous treatment, they would receive 100 U BOTOX
  - if the patient received 100 U BOTOX at the previous treatment, they would receive 200 U BOTOX
  - if the patient received 200 U BOTOX at the previous treatment, they would remain at 200 U BOTOX (after 2 requests to increase the dose from 200 U the patient will be exited; see below)

At the qualification for retreatment visit the investigator or designee will contact the IVRS/IWRS and indicate the treatment option for the patient. IVRS/IWRS options will be either to remain at the same dose or to increase the dose since patients will be exited from the study if the investigator assessed that a lower dose was warranted (see below).

In the following 2 scenarios patients will be exited once a minimum of 12 weeks follow-up since their last treatment has occurred:

- if the investigator requests a dose increase on 2 occasions for a patient already receiving 200 U, the IVRS/IWRS will indicate upon the second request that the patient must be exited from the study and further retreatment will therefore not be received.
- if the investigator assesses that the patient should not be retreated with the current dose but that a dose reduction would be warranted, the patient should be exited from the study as a reduction of dose in this study is not an option.

Once all "day of treatment criteria" have been met at the day of treatment visit, the study medication will be allocated via IVRS/IWRS. Study medication will be labeled with medication kit numbers and the IVRS/IWRS will provide the IDR with a specific medication kit number and treatment group assignment for the patient.

The patient number used in Study 191622-121 will be the same as that allocated to the patient in the preceding study, 191622-120.

5.6 Treatment Regimen and Dosing

Patients can receive multiple retreatments in this study.

All patients eligible for retreatment will receive either 50 U BOTOX (not to exceed 6 U/kg), 100 U BOTOX (not to exceed 6 U/kg), or 200 U BOTOX (not to exceed 6 U/kg). The dosage used at each retreatment will be determined as described in Section 5.5.

To qualify for retreatment a patient must fulfill the qualification for retreatment criteria (see Section 5.10.1 for details).

Each retreatment will also require all the day of treatment criteria to be fulfilled (see Section 5.9.1 for details).

5.7 Storage of Study Medications/Treatments

The study medication must be stored in a secure area and administered only to patients entered into the clinical study, at no cost to the patient, in accordance with the conditions specified in this protocol.

[redacted]

5.8 Preparation of Study Medications/Treatments

Study medication should be prepared once all the "day of treatment criteria" have been fulfilled, and the IVRS/IWRS has been contacted. It will be prepared in accordance with the instructions for reconstitution and preparation of study medication provided in the Pharmacy Manual.

An IDR must prepare the study medication. The IDR must be trained and have the skills necessary to prepare the study medication (eg, pharmacist, nurse, study coordinator). This person must not be associated or involved with a study patient's care or study assessments, with the exception of study medication preparation.

5.9 Treatment Administration

5.9.1 Day of Treatment Criteria

Treatment will be administered within 4 weeks of qualification for retreatment (see Section 5.10.1 for qualification for retreatment criteria), but no later than 48 weeks since study enrollment on day 1 of this study. The following "day of treatment criteria" must be fulfilled prior to each administration of study medication:

- patient does not have a UTI, in the opinion of the investigator (taking into account patient symptoms, presence of significant leukocyturia at screening (e.g. ≥ 30 WBC/HPF), urine culture results, need for antibiotic treatment,etc)
- appropriate prophylactic antibiotics have been initiated (see Section 5.9.2)
- antiplatelet or anticoagulant therapy or medications with anticoagulative effects have been discontinued at least 3 days prior to treatment
- negative urine pregnancy result (for postmenarche females)
- investigator continues to deem treatment is appropriate and no condition or situation exists which, in the investigators opinion, puts the patient at significant risk from receiving retreatment

Note: If a patient does not fulfill the "day of treatment criteria", they would still be considered qualified for retreatment (ie, qualification for retreatment or any associated procedures are not to be repeated). The treatment administration visit would be rescheduled for as soon as possible (if applicable), and the day of treatment criteria would need to be fulfilled prior to treatment administration.

5.9.2 Prophylactic Antibiotics

All patients must receive prophylactic antibiotics prior to each treatment administration. The approach is dependent upon the clinical judgment of the investigator, but could include either an intravenous (IV) dose of antibiotics prior to treatment administration on day 1 or oral antibiotics for at least 1 to 3 days prior to treatment and on the day of treatment. Antibiotics could also be continued for 1 to 3 days posttreatment (or longer).

Note: Independent from the above description for prophylactic antibiotics, if a UTI is identified from the urinalysis/culture obtained during the qualification for retreatment period, the UTI must be treated with an antibiotic to which the identified bacteria is sensitive per

local site practice. As per the day of treatment criteria described in Section 5.9.1, the patient must not have a UTI on the day of treatment, in the opinion of the investigator.

5.9.3 Use of Anesthesia

Anesthesia will be used for all patients during the treatment administration. The type of anesthesia is dependent upon the age of the patient as described below.

Precautions for latex sensitivity or allergy will be taken in accordance with local site practice.

Appropriate precautions should also be taken for patients with a history of malignant hyperthermia.

- for all patients < 12 years of age:
    - general anesthesia (which could include conscious sedation) will be used. It will be administered per local site practice; however, the use of neuromuscular blocking agents is not permitted.
- for patients ≥ 12 years of age, either general anesthesia or the instillation of local anesthesia will be used:
    - general anesthesia (which could include conscious sedation) will be administered per local site practice; however, the use of neuromuscular blocking agents is not permitted
    - local anesthesia to the bladder wall (with or without sedation) will be via instillation into the bladder of 1 to 2% lidocaine (or similar acting local anesthetic) prior to the procedure. The instillation solution should remain in the bladder for at least 15 minutes in order to achieve sufficient anesthesia. The bladder will then be drained of lidocaine, rinsed with saline, and drained again.

In addition, sedatives may be used if deemed medically necessary; their administration will be according to local site practice

The following are permitted to facilitate the insertion/removal of the cystoscope:

- lubricating gel
- local anesthesia to the urethra: intraurethral lidocaine gel (or similar local anesthetic gel)

5.9.4 Treatment Procedure

Precautions for latex sensitivity or allergy will be taken in accordance with local site practice.

A rigid or flexible cystoscope may be used for study treatment administration. As described above, lubricating gel and intraurethral lidocaine (or similar) can be used to facilitate cystoscope insertion. The bladder should be instilled with a sufficient amount of saline in order to achieve adequate visualization for the study injections.

The injection of study medication must not occur if bladder stones were identified during the qualification for retreatment visit from the bladder scan/ultrasound.

The investigator will receive one 10 mL syringe prefilled with 10 mL of study medication and one 1 mL syringe prefilled with saline.

The 10 mL of study medication will be administered as 20 injections each of 0.5 mL. Under direct cystoscopic visualization, injections should be distributed evenly across the detrusor wall and spaced approximately 1 cm apart. To avoid injecting the trigone, the injections should be at least 1 cm above the trigone (see the Study Treatment Injection Pattern diagram in Attachment 12.2). The injection needle should be filled (primed) with approximately 1 mL of reconstituted study medication prior to the start of injections (depending on needle length) to remove any air. The injection needle should be inserted approximately 2 mm into the detrusor for each injection. For the final injection site, a sufficient amount of saline (from the prefilled 1 mL syringe) will be flushed through the injection needle to deliver the small amount of study medication remaining in the needle. This will ensure that the entire volume of study medication is administered to the patient.

After the injections are given, the saline used for visualization should be drained from the bladder. Patients should remain in the clinic under observation for at least 30 minutes, or longer according to local site practice. Safety monitoring and assessments are to be done according to local site practice (eg, monitoring of blood pressure, pulse rate). Prior to leaving the study clinic, patients/parents/ caregivers will be instructed to contact the study site if they experience any adverse events posttreatment.

The investigator, or designee, will be required to document on the study treatment eCRF whether the study drug administration was performed as indicated above. In addition, details on equipment used (eg, rigid or flexible cystoscope) will be recorded.

5.9.5 Autonomic Dysreflexia

Patients with a spinal injury at thoracic level T5/6 or above or known history of autonomic dysreflexia should have their heart rate monitored during the treatment procedure and for a minimum of 30 minutes posttreatment. Should autonomic dysreflexia develop in a patient, the condition should be immediately handled according to local site practice. An occurrence of autonomic dysreflexia will be reported as an adverse event.

5.10 Retreatment

Patients can receive multiple retreatments in this study. For each retreatment, patients must fulfill the qualification for retreatment criteria described in Section 5.10.1. In addition, prior to treatment administration the day of treatment criteria must be fulfilled, as described in Section 5.10.1.

5.10.1 Qualification for Retreatment Criteria

At each follow-up clinic visit and telephone contact from week 12 onward, the patient's treatment response will be discussed with the patient/parent/caregiver.

Patients/parents/caregivers can request retreatment at any scheduled clinic or telephone visit, or between scheduled visits. If a request is made at a scheduled clinic visit and all "qualification for retreatment criteria" are fulfilled, that clinic visit then becomes the qualification for retreatment visit and the additional procedures will be performed, otherwise a qualification for retreatment clinic visit should be conducted within approximately 1 to 2 weeks of the request for retreatment and the "qualification for retreatment criteria" should be assessed prior to performing any other procedures. The reason for the request will be collected. (Note that patients who qualified for retreatment in the preceding study, 191622-120, at which point they exited, do not need to be requalified to receive their first retreatment in this study).

In order to qualify for retreatment, the criteria listed below must be fulfilled:

- patient/parent/caregiver requests retreatment
- patient has a total of at least 2 daytime urinary incontinence episodes over the 2-day diary collection period
- at least 12 weeks has elapsed since previous study treatment
- patient has not experienced a serious treatment-related adverse event at any time

Once these criteria are fulfilled, the patient is considered qualified for retreatment; this does not need to be repeated (or any of the associated qualification for retreatment procedures) if the patient does not get treated at the subsequent treatment visit or the treatment visit is delayed.

6. Response Measures and Summary of Data Collection Methods

6.1 Efficacy Measures

6.1.1 Bladder Diary Measures

The efficacy measure of main interest is the number of daytime urinary incontinence episodes as recorded in the 2-day bladder diary during the week preceding each study visit. The timepoint of main focus is week 6 after each treatment.

In addition, volume of urine at first morning catheterization and the occurrence of night time urinary incontinence will also be efficacy measures collected using the bladder diary.

Please refer to Section 6.3.5 for further details regarding the bladder diary.

6.1.2 Health Outcomes Measures

Two questionnaires will be utilized in this extension study:

[redacted]

- Modified Treatment Benefit Scale (Modified TBS)
    - the proportions of patients whose condition is rated as either ‘greatly improved’ or ‘improved’ will be determined

Please refer to Attachment 12.4 for further details regarding these questionnaires.

[redacted]

[redacted]

6.1.4 Duration of Effect Measures

The following 2 measures of duration of effect will be determined:

- time to patient request for retreatment
- time to patient qualification for retreatment

6.2 Safety Measures

- adverse events
- serious adverse events

[redacted]

6.3 Examination Procedures, Tests, Equipment, and Techniques

Once the parental/legal guardian consent, minor assent, and data authorization/protection forms have been obtained, and all the required inclusion and exclusion criteria at have been met, the patient will be considered enrolled in the study.

Evaluations should be performed by the same evaluator throughout the study whenever possible. If it is not possible to use the same evaluator to follow the patient, then it is preferable to have the evaluations overlap (examine the patient together and discuss findings) for at least one visit.

6.3.1 Latex Sensitivity or Allergy

Precautions for latex sensitivity or allergy will be taken in accordance with local site practice for any applicable procedures eg, urodynamics, blood sampling, as well as for the study treatment procedures.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.3.12 Health Outcome Measures

The [redacted] and the Modified TBS are both completed at weeks 6 and 12 after each treatment and at the qualification for retreatment visit (if the patient qualifies).

Questionnaires should be administered prior to the patient undergoing any procedure for any study visit and prior to study treatment and will be completed as described in Attachment 12.4. The same person(s) (patient or parent(s)/caregiver) should complete the questionnaires throughout the study where possible. For example, if the patient is able to complete the questionnaires themselves, they should complete all questionnaires themselves throughout the study. If a parent or caregiver will assist or complete on the patient's behalf, then this should be done throughout the study.

The versions of the questionnaires provided in the protocol (Attachment 12.4) are samples and will be replaced with the local language questionnaire for the country where the questionnaire will be administered.

[redacted]

[redacted]

[redacted]

6.4 Other Study Supplies

The following will be provided by Allergan:

- all supplies needed for urine pregnancy testing, blood and urine sampling (supplies for central laboratory urine analysis and urine culture and sensitivity)
- patient bladder diaries
- containers to measure volume of urine at first morning catheterization

The study sites will be responsible for providing the following supplies:

- prophylactic antibiotics required prior to study treatment
- sedatives and anesthesia for use during study treatment administration
- sterile saline (or other appropriate sterile fluid) for bladder visualization during cystoscopic procedures, and for reconstitution of study medication
- needles and syringes for reconstitution of study medication

- all necessary equipment to measure the required urodynamic parameters
- flexible or rigid cystoscope with injection port and needles for injection
- ultrasound for kidney and bladder assessment
- refrigerator to store dry/reconstituted study medication at a temperature of 2 to 8°C, monitored by a calibrated temperature recorder
- freezer (nonfrost free) to store immunogenicity serum samples at -20 ±5°C or below, monitored by a calibrated temperature recorder
- internet connection (high-speed connection) for eCRF completion

6.5 Summary of Methods of Data Collection

An IVRS/IWRS will be used to manage study medication inventory. Data will be collected using eCRFs via a validated electronic data capture system (EDC). Source documents will be used and stored at the sites, and may include a patient's medical records, hospital charts, clinical charts, patient chart, copy of the EDC file, as well as the results of diagnostic tests such as laboratory tests, ultrasounds, and urodynamics (if performed). A central laboratory will be used for the analysis of all blood and urine samples (only storage for immunogenicity samples). The data will be transferred via secure server to Allergan.

7. Statistical Procedures

The final statistical analysis will be conducted when all patients have completed or exited the study. On completion and analysis of the preceding study (191622-120), an interim analysis of this study is planned; sites may be unblinded upon completion of the interim analysis. A detailed statistical analysis plan will be finalized prior to the first study database lock.

7.1 Analysis Populations

One analysis population will be used in the statistical analysis of this study: the BOTOX-treated population.

Data from the patients' participation in this extension study (191622-121) will be integrated with the corresponding patients' data from the preceding study (191622-120). Thus, the BOTOX-treated population will include all patients enrolled into the extension study who have received at least 1 BOTOX treatment over the course of the total evaluation period.

All efficacy and safety analyses will be based on the treatment actually received in each treatment cycle. Patients will be grouped to the nearest dose group (50, 100, or 200 U BOTOX) based on the dose actually received.

7.2 Collection and Derivation of Efficacy Assessments

The key efficacy measure is the number of daytime urinary incontinence episodes recorded in the bladder diary. The diary data will be collected by the patient/parent/caregiver over 2 consecutive days in the week prior to clinic visits.

In addition, the bladder diary will be used to record the urine volume at first morning catheterization and the occurrence of night time incontinence.

Two questionnaires will be utilized in this extension study:

- [redacted]
- Modified TBS

[redacted]

7.2.1 Efficacy Variables

The following efficacy variables are being assessed in this long-term extension study:

- change from baseline in daily average frequency of daytime urinary incontinence episodes
- change from baseline in average urine volume at first morning catheterization (mL)

- presence or absence of night time urinary incontinence
- [redacted]
- proportion of patients with a positive treatment response on the Modified TBS (ie, rating their condition "greatly improved" or "improved")

[redacted]

The key efficacy variable is the change from baseline in daily average frequency of daytime urinary incontinence episodes (daytime is defined as the time between waking up to start the day and going to bed to sleep for the night). The daily average frequency of daytime urinary incontinence episodes is obtained using the total number of daytime urinary incontinence episodes recorded in a 2-day bladder diary divided by 2. Baseline is defined as the daily average frequency of episodes of daytime urinary incontinence prior to the initial study treatment in the preceding study, 191620-120. Each daytime period recorded in the bladder diary is normalized to represent a 12-hour period to account for differing durations of the daytime period. The daily average frequency of daytime urinary incontinence episodes will be adjusted by the normalized daytime period.

The timepoint of main interest is week 6 after each BOTOX treatment.

For the baseline and posttreatment data, a patient must have at least 1 day of diary data (defined as a day where there is 1 or more urinary episodes [eg, incontinence, catheterization, or voluntary void] during the daytime collection period [between waking to start the day and going to bed to sleep at night]). In the case of patients who partially complete their diary, providing that at least 1 valid diary day out of 2 is available, the 2-day frequency of daytime urinary incontinence will be prorated with the value from the valid diary day. If less than 1 diary day out of 2 has been completed, the frequency of daytime urinary incontinence will be considered as missing.

[redacted]

7.3 Hypothesis and Methods of Analysis

There will be no hypothesis testing in this long-term extension study. All data will be summarized with descriptive statistics and/or frequency tables.

7.3.1 Efficacy Analyses

The efficacy analysis will be based on the BOTOX-treated population. Week 6 after each treatment will be the timepoint of main interest and the efficacy variable of key focus is change from baseline in the daily average frequency of daytime urinary incontinence episodes. Data will be presented by BOTOX treatment cycle according to the dose received at that treatment cycle (grouped to the nearest dose group, ie, 50, 100 or 200 U BOTOX), as well as by an overall BOTOX group (ie, regardless of dose).

7.3.1.1 Efficacy Analyses for Daytime Urinary Incontinence Episodes

For each BOTOX treatment cycle, descriptive statistics will be provided for the daily average frequency of daytime urinary incontinence episodes at baseline and posttreatment visits. The change from baseline (arithmetic mean and least-squares [LS] mean) and the 95% confidence intervals (CI) of the arithmetic and LS mean change will be provided.

A responder analysis for daytime urinary incontinence will be performed using different thresholds of reduction from baseline. A patient will be considered a treatment responder if they have at least a 50% reduction from baseline in daytime urinary incontinence, however other thresholds will also be evaluated. The proportion of patients with $\geq$ 50%, $\geq$ 75%, $\geq$ 90%, and 100% reduction from baseline in daytime urinary incontinence will be presented by BOTOX treatment cycle for each posttreatment visit.

In addition the change from baseline and responder analyses will be performed using the normalized daily average frequency of daytime urinary incontinence episodes; these analyses will also be conducted without the normalization of the variable to a 12 hour daytime period.

7.3.1.2 Efficacy Analyses for the Average Urine Volume at First Morning Catheterization

For each BOTOX treatment cycle, descriptive statistics will be provided for the average urine volume at first morning catheterization at baseline and posttreatment visits as described in Section 7.3.1.1.

7.3.1.3 Efficacy Analyses for the Presence or Absence of Night Time Urinary Incontinence

For each BOTOX treatment cycle, the number and proportion of patients who experienced night time urinary incontinence on 0, 1, or 2 nights will be presented for baseline and posttreatment visits.

7.3.1.4 Health Outcomes Parameters

Health outcomes questionnaires and measures will be analyzed according to scoring algorithms described in the detailed statistical analysis plan.

[redacted]

For the Modified TBS, the proportion of patients with a positive treatment response (defined as their condition being either “greatly improved” or “improved”) will be presented and its 95% CI will be provided for each BOTOX treatment cycle at baseline and posttreatment visits.

[redacted]

[redacted]

7.3.1.6 Dose-response

Exploratory analysis may be performed to study dose-response based on the daily average frequency of daytime urinary incontinence episodes. Details for any dose-response analysis will be provided in the statistical analysis plan.

7.3.1.7 Duration of Effect

Duration of treatment effect will be assessed as time from each study drug administration to request for retreatment. The time from the day of each BOTOX treatment to the request for the subsequent treatment will be estimated using the Kaplan-Meier survival method for each treatment group for each BOTOX treatment cycle. For those patients who did not request retreatment, their data will be censored using the date of their last study visit. The proportions of patients/parents/caregivers requesting retreatment in each BOTOX treatment cycle will also be presented.

In addition, time to qualification for retreatment will be presented and analyzed as described above for time to request for retreatment.

7.4 Safety Analyses

All safety analyses will be conducted on the BOTOX-treated population. Safety variables are adverse events, serious adverse events, physical examination, vital signs, laboratory tests (urinalysis, hematology and clinical chemistry), renal function, kidney and bladder ultrasound, concomitant medications, concurrent procedures, and pregnancy test for females who are postmenarche.

Medical Dictionary for Regulatory Activities (MedDRA) nomenclature will be used to code adverse events. For each adverse event reported, the number and percent of patients will be tabulated based on the preferred term. The tables will be generated by relationship to treatment as well as by primary system organ class and severity.

Data will be presented by BOTOX treatment cycle and grouped according to the actual dose received at that treatment cycle (grouped to the nearest dose group [50, 100, or 200 U BOTOX]), as well as by an overall BOTOX group (ie, regardless of dose).

[redacted]

7.5 Subgroup Analyses

For each BOTOX treatment cycle, descriptive statistics will be provided for the daily average frequency of daytime urinary incontinence episodes as described in Section 7.3.1.1 by investigator site, as well as by key demographic or baseline characteristics, including concurrent anticholinergic therapy (eg, use and nonuse), baseline daytime urinary incontinence episodes (≤ 6 episodes or > 6 episodes over the 2-day diary collection period), age (< 12 years or ≥ 12 years), race, and sex.

7.6 Sample Size Calculation

The sample size calculation for this study is determined empirically. Approximately 100 patients are anticipated to roll over into this study, which is assuming approximately 76% of patients randomized into Study 191622-120 will be available and willing to participate in this study.

7.7 Interim Analyses

An interim analysis is planned to coincide with the completion and subsequent database lock of the main study, 191622-120. On completion of this interim analysis, the study will be unblinded to Allergan personnel. Study sites will be unblinded upon finalization of the interim clinical study report. Additional interim analyses may also be conducted. Further details of the interim analysis will be provided in the analysis plan.

[redacted]

8.1 Patient Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective patients as defined by the criteria in Sections 4.3 and 4.4 (Inclusion/Exclusion Criteria) will be considered for entry into this study. Patients will roll over directly into this

study from the preceding study, 191622-120 (the exit visit of the preceding study will be the same as the entry visit for this extension study).

8.1.2 Informed Consent and Patient Privacy

The study will be discussed with the patient/legally authorized representative and a patient wishing to participate or his/her legally authorized representative must give informed consent and, when applicable, minor assent prior to any study-related procedures or change in treatment. The patient/legally authorized representative must also give authorization (US only), data protection consent (Europe only), and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related activities or procedures.

As patients directly roll over from Study 191622-120 to this extension study, consent will have been obtained prior to the patient exiting the preceding study, 191622-120.

Further information is provided in Section 10.1.

Each patient who provides informed consent and/or assent will continue to use their IVRS/IWRS-assigned patient number from Study 191622-120 and this will be used on patient documentation throughout the study.

8.1.3 Procedures for Final Study Entry

Final study eligibility will be determined at the day 1 visit to confirm that the patient fulfills all the inclusion criteria without any exclusion criteria as specified in Sections 4.3 and 4.4 of the protocol.

Entry into this study is directly from the exit visit from the preceding study, 191622-120 (exit visit of Study 191622-120 equals day 1 for Study 191622-121), therefore procedures associated with the exit visit of the preceding study do not need to be repeated for entry into this study. Similarly, if a patient entered this extension study having qualified for retreatment in the preceding study, the qualification procedures do not need to be repeated in this study.

A patient is considered to have entered (ie, enrolled) into the study when they have met the study entry criteria.

[redacted]

8.3 Instructions for the Patients

Patients/parents/caregivers will be instructed on the following:

- to strictly follow the study visit schedule and report any changes in condition to the investigative site
- to maintain the dose of any concurrent medication and anticholinergic medication during the study whenever possible (except anticholinergic medication which can be modified as described in Section 4.5.1)
- to remain on the same CIC regimen
- to change wet pads/diapers/underwear as soon as possible during diary collection periods in order to accurately capture episodes of incontinence
- to call the study site if they are experiencing any difficulties following study treatment administration or study procedures
- to contact the study site to report any hospitalizations
- to call the study site as soon as possible in order to reschedule, if the patient cannot make their next scheduled study visit
- diaries should be completed and brought to the study site at each scheduled clinic study visit

8.4 Unscheduled Visits

Unscheduled visits can be performed if safety concerns arise and at the discretion of the investigator. Additional examinations may be performed as necessary to ensure the safety

and well being of patients during the study. eCRFs will be completed for each unscheduled visit.

8.5 Compliance with Protocol

Participating patients (or parents/caregivers) should be able to adhere to the diary completion and testing parameters as described in this protocol.

Data will be recorded on the appropriate eCRF supported by appropriate source documentation. At each visit, patients/parents/caregivers should be asked if any concomitant medications had been used, if they had undergone any concurrent procedures (non-study procedures), and their compliance with the protocol since the previous visit.

8.6 Early Discontinuation of Patients

Patients may voluntarily withdraw from the study at any time. Patient discontinuation from the study and the reason for early discontinuation will be clearly documented on the appropriate eCRF. Patients who agree to follow-up will be followed for a minimum of 12 weeks after study treatment for safety as per the protocol. If a patient exits the study prior to study completion, all assessments for that visit should be performed in addition to any other exit visit assessments.

8.7 Withdrawal Criteria

Patients have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or the institution. The investigator and Allergan also have the right to withdraw a patient from the study at any time for any reason.

Patients should be discontinued from the study if any of the following criteria are met. Where possible, the decision to withdraw a patient from study treatment or the study should be discussed with Allergan.

- patient develops (or has an exacerbation of) any medical condition that, in the opinion of the investigator, would put the patient at an unacceptable medical risk or compromises the patient's ability to participate in the study
- patient becomes pregnant (see Section 4.5.1.1 Definition of Females of Childbearing Potential and Acceptable Contraceptive Methods)

- patient/parent/caregiver is unwilling or unable to continue to comply with study procedures
- investigator requests a dose increase after the patient has received 2 treatments with 200 U BOTOX
- investigator assesses that the patient should not be retreated with the current dose, but that a dose reduction would be warranted

8.8 Study Termination

The study may be stopped at his/her study site at any time by the site investigator. Allergan may stop the study (and/or the study site) for any reason with appropriate notification.

9. Adverse Events

Throughout the course of the study, all adverse events will be monitored and reported on an adverse event case report form, including seriousness, severity, action taken, and relationship to study drug or injection procedure. If adverse events occur, the first concern will be the safety of the study participants.

Any adverse event that is recorded as ongoing at exit from the preceding study (191622-120) that is still ongoing at entry into this study will be recorded.

9.1 Definitions

9.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Note: Adverse events must be collected once informed consent has been obtained, regardless of whether or not the patient has been administered study drug.

Progression of NDO, including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and /or lack of efficacy, should not be reported as adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

Adverse events will be assessed, documented, and recorded in the eCRF throughout the study (ie, after informed consent/assent has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each patient or parent/caregiver a general, non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the appropriate eCRF.

9.1.2 Definition of Adverse Events of Urinary Tract Infection and Urinary Retention

Study-specific definitions for the adverse events of UTI and urinary retention are provided below.

Adverse Event of Urinary Tract Infection

An adverse event of UTI is defined as being a symptomatic UTI that requires treatment in the opinion of the investigator.

Note: If urinalysis/culture results are reported which, in the opinion of the investigator, are considered clinically significant but do not fulfill the above definition of a UTI, the findings should be recorded as adverse events (eg, bacteriuria, leukocyturia).

Adverse Event of Urinary Retention

Urinary retention should only be reported in patients who had the ability to spontaneously void between catheterizations prior to study treatment. It is defined in these patients as the inability to spontaneously void for at least 24 hours, which is not in conjunction with the patient experiencing constipation.

9.1.3 Serious Adverse Event

A serious adverse event is any adverse event occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (see Section 9.3 for procedures for reporting a serious adverse event).

Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or non spontaneous) as a serious adverse event.

Preplanned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization is not reportable as a serious adverse event.

Any preplanned surgery or procedure should be clearly documented in the site source documents by the medically qualified investigator at the time of the patient's entry into the study. If it has not been documented at the time of the patient's entry into the study, then it should be documented as a serious adverse event and reported to Allergan.

9.1.4 Severity

A clinical determination will be made of the intensity of an adverse event. The severity assessment for a clinical adverse event must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.
Not applicable	In some cases, an adverse event may be an 'all or nothing' finding which cannot be graded.

9.1.5 Relationship to Study Drug or Study Procedure

A determination will be made of the relationship (if any) between an adverse event and the study drug or study procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug or study procedure.

9.2 Procedures for Reporting Adverse Events

Any adverse event must be recorded on the appropriate eCRF.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Investigator's Brochure) must be reported to the governing IRB/IEC as required by the IRB/IEC, local regulations, and the governing health authorities. Any adverse event that is marked 'ongoing' at the exit visit must be followed-up as appropriate.

9.3 Procedures for Reporting a Serious Adverse Event

Any serious adverse event occurring during the study period (beginning with informed consent/assent and until study exit or early termination) and for at least 12 weeks after the last dose of study drug must be immediately reported but no later than 24 hours after learning of a serious adverse event. Serious adverse events must be reported to Allergan (or agent of Allergan) as listed on the Allergan Study Contacts Page and recorded on the Serious Adverse Event form. All patients with a serious adverse event must be followed up and the outcomes reported. The investigator must supply Allergan and the IRB/IEC with any additional requested information (eg, autopsy reports and discharge summaries).

In the event of a serious adverse event, the investigator must:

1. notify Allergan immediately by fax or e-mail using the Serious Adverse Event form (contact details can be found on page 1 of the Serious Adverse Event form); phone numbers and relevant Allergan personnel contacts are also on the front page of this protocol and the Study Contacts Page.
2. obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient
3. provide Allergan with a complete, written description of the adverse event(s) on the Serious Adverse Event form describing the event chronologically, including any treatment given (eg, medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course, and relevant clinical laboratory tests, etc. Include any additional or alternative explanation(s) for the causality, which includes a statement as to whether the event was or was not related to the use of the investigational drug
4. promptly inform the governing IRB/IEC of the serious adverse event as required by the IRB/IEC, local regulations, and the governing health authorities

9.4 Procedures for Unblinding of Study Medication

When necessary for the safety and proper treatment of the patient, the investigator can unblind the patient's treatment assignment to determine which dosage of BOTOX has been assigned and institute appropriate follow-up care. When possible, the Allergan Medical Safety Physician should be notified prior to unblinding study medication. The investigator should inform the Allergan Medical Safety Physician of the unblinding if there is no notification prior to the unblinding.

The treatment assignment for the patient can be determined by designated site personnel calling into the IVRS or IWRS system via password protected access. The reason for breaking the code must be recorded in the patient's source documents.

10. Administrative Items

This protocol is to be conducted in accordance with the applicable Good Clinical Practice (GCP) regulations and guidelines, eg, the International Conference on Harmonisation (ICH) guideline on GCP.

10.1 Protection of Human Subjects

10.1.1 Compliance with Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations

Written informed consent/assent is to be obtained from each patient and/or from the patient's legally authorized representative prior to initiating any study-related activity or procedure. If the patient is under the legal age of consent, the consent form must be signed by the legally authorized representative in accordance with the relevant country and local regulatory requirements.

Written parental/legal guardian informed consent in addition to a separate written minor consent and/or assent (in accordance with any applicable state and local laws/regulations) are required for each minor study patient prior to study enrollment or any study-related procedures in the study.

10.1.2 Compliance With IRB or IEC Regulations

This study is to be conducted in accordance with IRB regulations (US 21 CFR Part 56.103) or applicable IEC regulations. The investigator must obtain approval from a properly constituted IRB/IEC prior to initiating the study and re-approval or review at least annually. Allergan is to be notified immediately if the responsible IRB/IEC has been disqualified or if proceedings leading to disqualification have begun. Copies of all IRB/IEC correspondence with the investigator should be provided to Allergan.

10.1.3 Compliance With Good Clinical Practice

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

10.1.4 Compliance With Electronic Records; Electronic Signatures Regulations (US 21 CFR Part 11)

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

10.2 Changes to the Protocol

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.3 Patient Confidentiality

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the subject's name will not be disclosed in these documents. The patient's name may be disclosed to the Sponsor of the study, Allergan, or the governing health authorities or the US Food and Drug Administration (FDA) if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

10.3.1 Patient Privacy

Written authorization (US sites only), data protection consent (European sites only), and other documentation in accordance with the relevant country and local privacy requirements (where applicable) is to be obtained from each patient prior to and study-related procedure, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information ("HIPAA"), European Union Data Protection Directive 95/46/EC ["EU Directive"]).

In accordance with HIPAA requirements, additional purposes of this study may include the publishing of anonymous patient data from the study.

10.4 Documentation

10.4.1 Source Documents

Source documents may include a patient's medical records, hospital charts, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests such as x-rays, laboratory tests, ultrasounds, and electrocardiograms. The investigator's copy of the eCRF serves as part of the investigator's record of a patient's study-related data.

The following information should be included in the patient's medical record:

- patient's name
- patient's contact information
- a statement that informed consent and/or assent was obtained (including the date). A statement that written authorization (US sites only), data protection consent (EU sites only), or other country and local patient privacy required documentation for this study has been obtained (including the date)
- date that the patient entered the study and patient number
- study title and/or the protocol number of the study, and the name of Allergan
- dates of all patient visits
- date and details of study treatment administration
- date(s) of patient request for retreatment
- reason for dose option
- medical and surgical history (including prior medications for treatment of NDO)
- all concurrent medications (list all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded).
- occurrence and status of any adverse events (including any procedure-related adverse events)
- date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation
- results of laboratory tests performed by the central laboratory

- the results of laboratory tests performed by the site (eg, urine pregnancy test)
- urodynamic tracings, if urodynamic assessment performed
- results of bladder and kidney ultrasound
- concurrent procedures performed during the study
- vital signs and physical examination findings
- height and weight

The responses to the following questionnaires/assessments entered directly onto the appropriate form will be considered source data:

- bladder diary
- primary reason for requesting retreatment
- [redacted]
- Modified TBS

In addition, study drug accountability and reconstitution records (stored separately with the IDR in order to maintain blinding status for site staff with direct contact with patient and/or data) will be retained as source documentation.

10.4.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each patient's eCRF and related documents in a timely manner. An investigator who has signed the protocol signature page should electronically sign for the eCRFs (as indicated in the eCRFs) to ensure that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be submitted to Allergan in a timely manner, or as otherwise specified by Allergan, and will be maintained in a central data repository.

10.4.3 Study Summary

An investigator's summary will be provided to Allergan within a short time after the completion of the study, or as designated by Allergan. A summary is also to be provided to the responsible IRB/IEC.

10.4.4 Retention of Documentation

All study related correspondence, patient records (ie, source documents listed in Section 10.4.1), consent forms, patient privacy documentation, records of the distribution and use of all investigational products, bladder diaries, questionnaires, correspondence with the IRB/IEC, and other essential documents should be maintained on file.

For countries falling within the scope of the ICH guidelines, the Allergan-specific essential documents should be retained until 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 investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s), or if needed by Allergan.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

Allergan requires that it be notified in writing if the investigator wishes to relinquish ownership of the data so that mutually agreed-upon arrangements can be made for transfer of ownership to a suitably qualified, responsible person.

10.5 Labeling, Packaging, and Return or Disposal of Study Medications/Treatments

10.5.1 Labeling/Packaging

The investigational materials will be packaged and labeled in identically appearing vials. The study treatment will be identified as an investigational compound. The study number and kit number will be identified on the carton.

10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units (ie, number of vials) received from Allergan, dispensed to the patients, the number of units returned to the Allergan or Allergan designee during and at the completion of the study. A detailed inventory must be completed for the study medication. The study medication must be reconstituted and administered only by appropriately qualified persons to patients in the study. The medication is to be used in accordance with the protocol under the direct supervision of an investigator.

10.5.3 Return or Disposal of Study Medications/Treatments and/or Supplies

All clinical study medications/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction, or destroyed at the site as specified in writing by Allergan.

10.6 Monitoring by the Sponsor

A representative of Allergan will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the study.

Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

10.7 Handling of Biological Specimens

Samples of blood and urine, for evaluation of hematology, chemistries, and urinalysis, will be analyzed at a centralized clinical laboratory with certification from a recognized accreditation agency (eg, College of American Pathology or Clinical Laboratory Improvement Amendments certification).

The central laboratory manual provides details regarding laboratory collection and shipment procedures for blood and urine samples in this study.

Allergan shall have full ownership rights to any biological samples derived from the study.

10.8 Publications

Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between the investigators and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

10.9 Coordinating Investigator

A signatory coordinating investigator will be designated prior to the writing of the clinical study report.

11. References

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12. Attachments

[redacted]

12.2 Study Treatment

[redacted]

12.4 Health Outcomes Questionnaire Descriptions and Instructions

12.5 Glossary of Abbreviations

12.6 Protocol Amendment 1 Summary

12.7 Protocol Amendment 2 Summary

12.1 Preparation of Study Medication

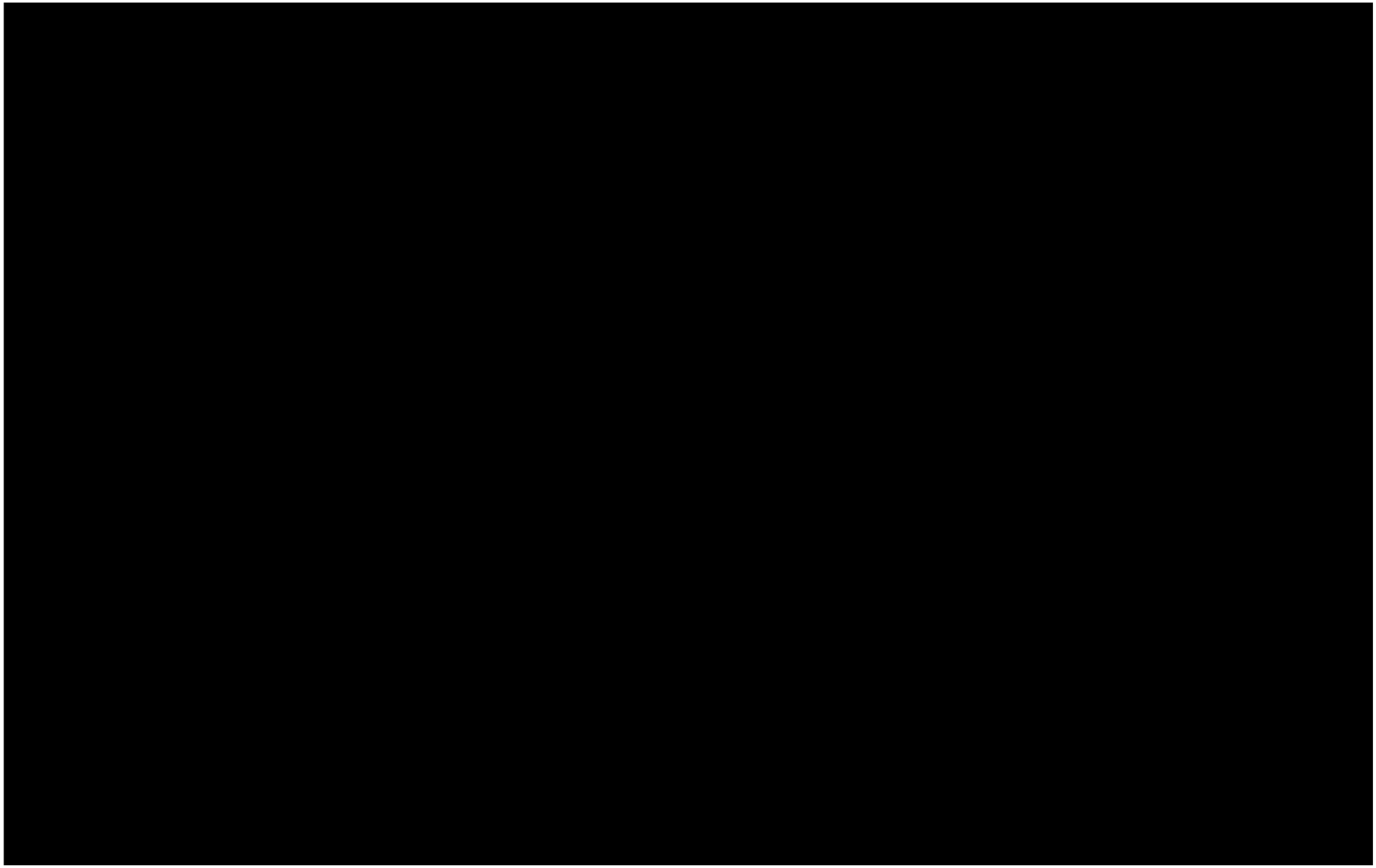
Study medication vials will be reconstituted for the 50, 100, and 200 U BOTOX dose groups (not to exceed 6 U/kg) based on the tables in the following sections.

When reconstituting study medication for each patient, sterile, preservative-free, normal saline (diluent) should be added to the BOTOX vial with a new 10-mL syringe. The vacuum within the vial will draw in the diluent. Do not use the vial if a vacuum is not observed. Instead, contact IVRS/IWRS to allocate a replacement kit and notify Allergan personnel of the situation.

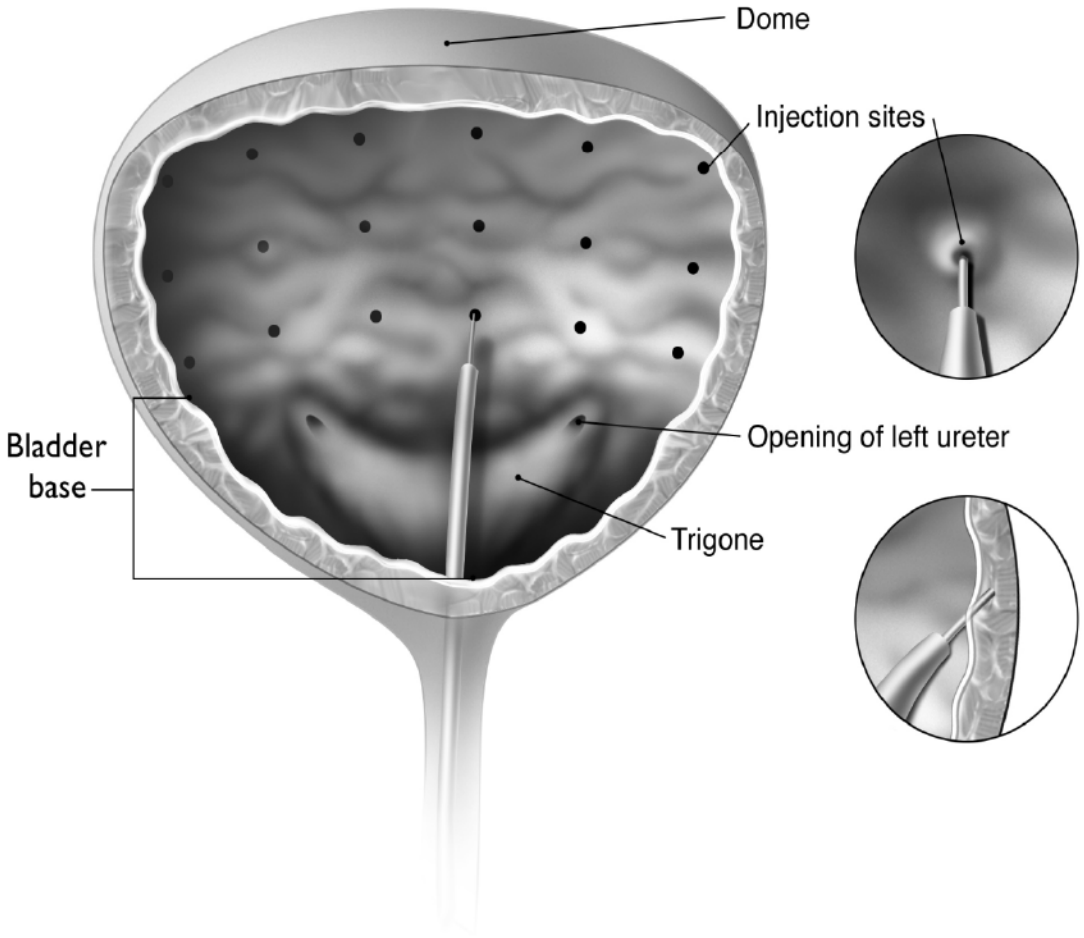
Once the diluent has been drawn into the vial, the vial should be rotated gently to mix the contents. The reconstituted study medication should be clear, colorless and free of particulate matter.

A new 10-mL syringe should be used to withdraw the required solution from the study medication vial. This will be the dosing syringe. The reconstitution is completed by adding to the dosing syringe, the additional amount of saline required to make the final concentration. A detailed step-by-step process for study medication reconstitution will be provided in a Pharmacy Manual.

[redacted]



12.2 Study Treatment Injection Pattern



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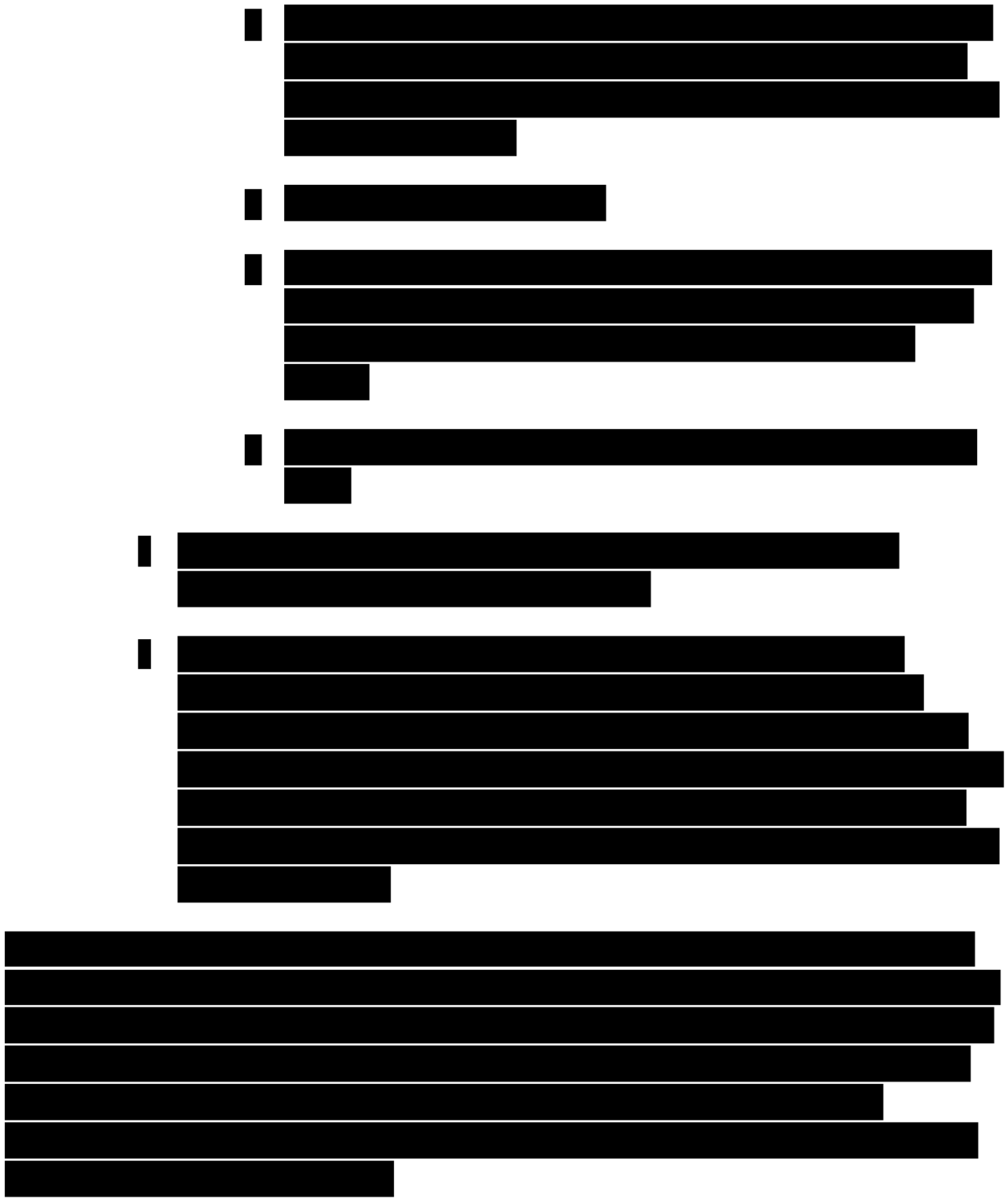

[redacted]

12.4 Health Outcomes Questionnaire Descriptions and Instructions (and Modified TBS)

Patient questionnaires will be:

- administered to all patients in the study prior to having any study procedure performed
- completed by the patient (parent or caregiver can also complete) using a black, ballpoint pen on a firm writing surface. The same person(s), (patient or parent(s)/caregiver), should complete the questionnaires throughout the study where possible.
- administered in a quiet place with ample time for the patient to complete the questionnaire
- filled out completely (every question must be answered)
- initialed and dated on the last page by the patient/parent/caregiver who completed the questionnaire
- completed only at protocol-specified study visits (no attempt should be made at any subsequent visit to administer missed questionnaires)
- a source document; please do not make or use any photocopies of the forms

- checked for completeness, and not content, in the patient's presence - study site personnel should not change responses on the questionnaires

The versions of the questionnaires provided in the protocol are samples and will be replaced with a translation of the questionnaire in the local language for the country where the questionnaire will be administered.

[redacted]

[redacted]

Modified Treatment Benefit Scale

The TBS is single-item scale designed to assess the change in the patient's OAB condition following treatment (Colman et al, 2008). The patients current condition (urinary problems, urinary incontinence) is compared to their condition prior to receipt of any study treatment. The TBS was modified for this study based on parent/caregiver and patient input on the Pediatric Diary to adapt it for use in a pediatric population. The questionnaire can be completed by patients, parents, or caregivers, and this will be indicated on the questionnaire.

Patients/parents/caregivers respond to the following:

Please write down what you think about how much you leak urine (pee) now compared to how much you leaked urine (pee) ***before you had any study treatment in the PREVIOUS trial.***

Leaking urine (pee) has

- ☐ *greatly improved*
- ☐ *improved*
- ☐ *not changed*
- ☐ *worsened*

since I had any study treatment

12.5 Glossary of Abbreviations

Term/Abbreviation	Definition
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AUC	area under the curve
BOTOX®	Botulinum Toxin Type A Purified Neurotoxin Complex (US adopted name onabotulinumtoxinA), referred to as BOTOX
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIC	clean intermittent catheterization
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
DLPP	detrusor leak point pressure
DRC	Data Review Committee
EBC	expected bladder capacity
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELISA	enzyme linked immunosorbent assay
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEENT	head, eyes, ears, nose, throat
HIPAA	Health Insurance Portability and Accountability Act
HRQOL	health-related quality of life
ICH	International Conference on Harmonisation
IDC	involuntary detrusor contraction
IDR	independent drug reconstitutor
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system

LS	least squares
MCC	maximum cystometric capacity
mITT	modified intent-to-treat
NDO	neurogenic detrusor overactivity
OAB	overactive bladder
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PP	per protocol
RBC	red blood cell
SD	standard deviation
SNAP-25	synaptosomal protein of molecular weight 25 kDa
SNARE	soluble NSF [N-ethylmaleimide-sensitive factor] attachment protein receptor
T1	thoracic vertebra level 1
TBS	Treatment Benefit Scale
TRPV1	transient receptor potential vanilloid 1
UDS	urodynamic studies
US	United States (of America)
UTI	urinary tract infection
WBC	white blood cell

12.6 Protocol Amendment 1 Summary

Title: Long-term Extension Study of BOTOX® in the Treatment of Urinary Incontinence Due to Neurogenic Detrusor Overactivity in Patients 8 to 17 Years of Age

Protocol 191622-121 Amendment 1

Date of Amendment: October 2013

Amendment Summary

This summary includes changes made to Protocol 191622-121 (14 January 2013).

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Protocol Title Page	Removed emergency contact number	This information is now included in a study specific contacts page
Investigator signature page	Removed Study Location Added text to ensure all participating personnel are adequately informed about the protocol Removed provision for multiple investigator signatures	Global change to Allergan's protocol template
Synopsis/4.4 Exclusion Criteria/4.5.2 Prohibited Medications/Treatments	Clarified that indwelling catheters are permitted overnight if needed, but that indwelling catheterization is not permitted during diary collection periods	The use of an indwelling catheter overnight is common practice in the patient population intended to be recruited to this study; therefore their use is allowed. However, since the first morning catheterization urine volume is an efficacy parameter, as well as presence or absence of nighttime incontinence, indwelling catheters will not be allowed during diary collection periods.
[redacted]	[redacted]	[redacted]

Section	Revision	Rationale
4.5.1.1 Definition of Females of Childbearing Potential and Acceptable Contraceptive Methods	Removed text relating to females becoming sexually active when postmenarche	Females who are postmenarche are considered to be of childbearing potential in a biological context; therefore text removed.
4.5.2 Prohibited Medications/Treatments	Clarified that indwelling catheter was permitted overnight if needed, but that indwelling catheterization was not permitted during diary collection periods	The use of an indwelling catheter overnight is common practice in the subject population intended to be recruited to this study; therefore their use is allowed. However, since the first morning catheterization urine volume is an efficacy parameter, as well as presence or absence of night time incontinence, indwelling catheters will not be allowed during diary collection periods.
5.9.4 Treatment Procedure	Added text to clarify that patients should remain under observation at the clinic for longer than 30 minutes if local site practice requires this	The protocol provides a minimum time period for observation after treatment; however, local site practice should take precedence if it requires a longer observation period.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
8.6 Early Discontinuation of Patients	Clarification added in relation to follow-up in patients who agree to follow-up after exiting the study early.	Clarification regarding time period of follow-up included based on Regulatory Agency feedback.
9.1.1 Adverse Event	Additional text regarding the documentation of disease progression/lack of efficacy	Global change to Allergan's protocol template
10.1.1 Compliance with Informed Consent Regulations (US 21 CFR Part 50) and Relevant Country Regulations	Amended wording	To reflect global change to Allergan's protocol template
[redacted]	[redacted]	[redacted]

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
12.5 Package Insert	Removed section	Global change to Allergan's protocol template

12.7 Protocol Amendment 2 Summary

Title: Long-term Extension Study of BOTOX® in the Treatment of Urinary Incontinence Due to Neurogenic Detrusor Overactivity in Patients 5 to 17 Years of Age

Protocol 191622-121 Amendment 2

Date of Amendment: April 2016

Amendment Summary

This summary includes changes made to Protocol 191622-121 (4 October 2013).

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Title and Study Population	Changed minimum age to 5	Updated patient inclusion criterion
[redacted]	[redacted]	[redacted]
Inclusion criteria	Reduced minimum age requirement from 8 years old to 5 years old	Expand age range for inclusion in the study.
Section 5.9.1	Day of Treatment Criteria: added "or presence of significant leukocyturia (e.g. ≥ 30 WBC/HPF)" to the criteria which the investigator should consider when determining if the patient has a UTI	To ensure patient safety, added that in addition to considering patient symptoms, urine culture results and the need for antibiotic treatment, the investigator should also consider the presence of clinically significant leukocyturia when determining if the patient has a UTI. Also provided an example of clinically significant leukocyturia as ≥ 30 WBC/HPF.
Section 5.9.3	Use of Anesthesia: added "which could include conscious sedation"	For clarity
[redacted]	[redacted]	[redacted]

ALLERGAN

Protocol 191622-121 Amendment 2

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
[redacted]	[redacted]	[redacted]