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Study ID: 191622-120

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

Protocol Amendment 3 Date: 27 September 2017

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STUDY TITLE

BOTOX® in the Treatment of Urinary Incontinence Due to Neurogenic Detrusor Overactivity in Patients 5 to 17 Years of Age

Protocol Number:	191622-120 Amendment 3
EudraCT Number:	2012-004877-26
Phase:	3
Name of Investigational Product:	BOTOX®

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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

Table of Contents

List of Tables

List of Figures

Protocol Summary

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

Phase: 3

Study Objective: To evaluate the 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 of the treatment groups) has an acceptable safety profile when injected into the detrusor of patients 5 to 17 years of age with NDO. BOTOX (one or more of the treatment groups) improves the symptoms of NDO as measured by a reduction from baseline in daytime urinary incontinence episodes.

Study Design

Structure: Multicenter, randomized, double-blind, parallel group

Duration: Patients will participate in the study until one of the following exit criteria is met, whichever occurs sooner:

- patient has qualified for retreatment (retreatment to occur in the extension study, for patients who elect and qualify to enroll), or
- patient has completed 48 weeks after randomization/day 1, if never qualifies for retreatment (ie, completes the 48 week visit)

Study Treatment Groups: There will be 3 treatment groups:

- 50 U BOTOX (not to exceed 6 U/kg)
- 100 U BOTOX (not to exceed 6 U/kg)
- 200 U BOTOX (not to exceed 6 U/kg)

Controls: None

Dosage/Dose Regimen: A single treatment will be administered on day 1 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 (see Section 5.9.3 for details) 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.

Qualification for retreatment can occur in this study (see Section 5.10); however, the patient will exit this study once qualified for retreatment and treatment administration will occur in the extension study (patients who never qualify for retreatment can also enroll into the extension study once they complete this study [ie, 48 weeks from randomization/day 1]).

Randomization/Stratification: Patients will be randomized on day 1 to one of 3 treatment groups:

- 50 U BOTOX (not to exceed 6 U/kg)
- 100 U BOTOX (not to exceed 6 U/kg)
- 200 U BOTOX (not to exceed 6 U/kg)

Patients will be centrally randomized and assigned a randomization number prior to treatment. In order to ensure balance across treatment groups, patients will be stratified by age (< 12 years or ≥ 12 years), and baseline daytime urinary incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day diary collection period).

[redacted]

Study Population Characteristics

Number of Patients: Approximately 132 patients will be randomized at approximately 35 to 45 sites (40 patients per treatment group plus 10% dropout by the primary timepoint of week 6).

Condition/Disease: Urinary incontinence due to NDO

Key Inclusion Criteria:

[redacted]

- patient must be regularly using clean intermittent catheterization (CIC) to empty the bladder [redacted]

[redacted]

[redacted]

Key Exclusion Criteria:

[redacted]

- patient has had surgery of the spinal cord within 6 months of screening

[redacted]

- patient has cerebral palsy

[redacted]

- 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 treatment of NDO. (If a nonimplantable device is used, it must be discontinued at least 7 days prior to the first screening procedure; if a device is implanted, it must be inactive for at least 4 weeks prior to the first screening procedure; neither should be used during the study).
- patient uses 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)
- patient has had previous or current:
    - botulinum toxin therapy of any serotype for any urological condition, or
    - treatment with botulinum toxin of any serotype within 3 months of randomization/day 1 for any other condition or use

[redacted]

[redacted]

Response Measures

Efficacy:

Primary:

- daytime urinary incontinence episodes

Secondary:

- maximum cystometric capacity (MCC)
- presence/absence of an IDC
- if an IDC is present, maximum detrusor pressure during the first IDC ($Pdet_{Max1stIDC}$)
- maximum detrusor pressure during the storage phase ($Pdet_{Max}$)
- if a leak occurs, detrusor leak point pressure (DLPP)
- urine volume of first morning catheterization
- presence/absence of night time urinary incontinence
- time to patient request and time to qualification for retreatment

[redacted]

Safety:

- adverse events
- serious adverse events

[redacted]

General Statistical Methods and Types of Analyses: For efficacy variables, data will be analyzed using the modified intent-to-treat (mITT) population consisting of all randomized patients who receive treatment on randomization/day 1. Patients will be analyzed using their randomized treatment assignment except for those patients who triggered the 6 U/kg limit who will be grouped according to the nearest dose group (50, 100, or 200 U BOTOX) based on the dose actually received. The primary efficacy variable is the change from baseline at week 6 posttreatment in the daily average frequency of daytime urinary incontinence episodes, with baseline frequency defined as the daily average frequency of daytime urinary incontinence episodes preceding the study treatment.

For each of the BOTOX doses, descriptive statistics will be provided for the daily average frequency of daytime urinary incontinence episodes at baseline and week 6, including change from baseline. The treatment difference in mean change from baseline for 200 versus 50 U BOTOX and 100 versus 50 U BOTOX will be calculated. Pairwise comparisons of 200 versus 50 U BOTOX and 100 versus 50 U BOTOX at week 6, will be evaluated using an analysis of covariance (ANCOVA) model; a hierarchical analysis strategy to adjust for multiplicity will be used. A similar analysis, without a hierarchal testing strategy, will be applied to other timepoints and to the secondary efficacy variables (pairwise comparisons will be done up to week 12).

[redacted]

A preliminary estimate of duration of effect will be evaluated as time from treatment on day 1 to request for retreatment using a Kaplan-Meier survival analysis. Dose-response analyses will include a nonparametric area under the curve (AUC) analysis of daily average frequency of daytime urinary incontinence episodes.

The health outcomes parameters of PinQ and Modified TBS will be analyzed using either an analysis of variance (ANOVA) or ANCOVA for continuous variables, or using Pearson's chi-square test, Fisher's exact test (or CMH) for categorical variables as appropriate on the mITT population.

For safety variables, data from all patients who received study drug will be included; data will be analyzed using the dose actually received, with all patients allocated to the nearest dose group (50, 100, or 200 U BOTOX).

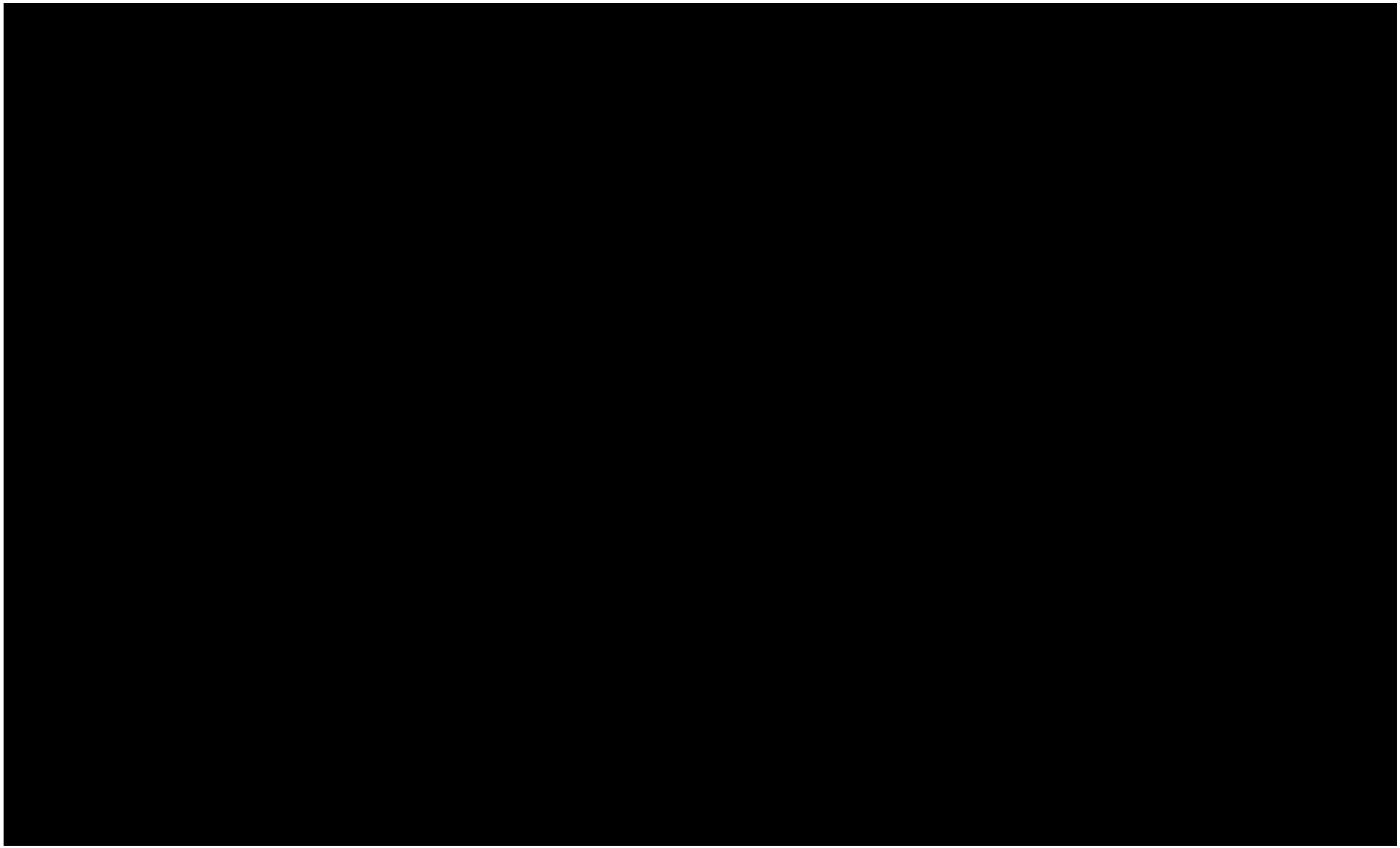
Sample Size Calculation: The sample size calculation for this study is determined empirically. A total of 34 patients per treatment group are to be randomized for the study (30 patients per treatment group plus additional patients to address patient attrition [estimated to be 10% by week 6]).

The following table displays the estimated distance for treatment differences between 200 U BOTOX (maximum 6 U/kg) and 50 U BOTOX (maximum 6 U/kg) in mean daily average frequency of daytime episodes of urinary incontinence change from baseline at week 6 for a range of common standard deviations (SD). All calculations assume 30 patients per treatment group and a 2-sided test significance level of 0.05. The calculation was performed using the commercial software nQuery Advisor (procedure MTC0-1), version 6.01, and the confidence interval is based on the large sample z statistic.

Standard Deviation	Distance From Mean to the Limit
2.0	1.012
2.5	1.265
3.0	1.518
3.5	1.771
4.0	2.024

Note: The ranges of the SDs are determined based on the values from the adult pivotal phase 3 studies (191622-515 and 191622-516). The estimate of the SD for the 200 U BOTOX treatment group is 3.44 for Study 191622-515, 2.58 for Study 191622-516, and 3.10 for the 2 studies combined.

[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 (CNS).

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 CNS 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, where 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, where 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 shared common feature 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 be 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 (Botulinum Toxin Type A purified neurotoxin complex [US adopted name onabotulinumtoxinA], referred to as 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. Thus, BOTOX 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 BOTOX.

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). Currently, Study 191622-094 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. No clinically relevant difference was observed between the 200 and 300 U BOTOX 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 posttreatment. 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 BOTOX 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 treatment.

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 purpose of Study 191622-120 is to assess the safety and efficacy of BOTOX for the treatment of urinary incontinence in the NDO pediatric population. On completion of this study, patients will also have the opportunity to roll-over into an extension study and receive retreatment (Study 191622-121).

The pediatric population to be studied, following discussion with the United States Food and Drug Administration (US FDA), was defined as patients aged 8 to 17 years, as the age group needed to be sufficiently bothered by urinary incontinence to be in line with the adult indication of urinary incontinence due to NDO. However, 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. 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.

The doses selected in this pediatric study provide a sufficient range to assess dose-response while not exceeding the adult dose of 200 U BOTOX. In addition, an upper cap of 6 U/kg BOTOX is in place to ensure maintenance of a safety margin based on nonclinical studies. There are data from published literature in which doses above those proposed in this study have been used in the pediatric population (eg, 300 U and 10 U/kg [Gamé et al, 2009; Sager et al, 2012]). However, dose-ranging studies in the pediatric NDO population have not been conducted and it would not be appropriate to exceed the dose for the adult indication ie, 200 U.

2 Study Objectives and Clinical Hypotheses

2.1 Study Objectives

The objectives of this study are to evaluate the 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 (1 or more of the treatment groups) has an acceptable safety profile when injected into the detrusor of patients 5 to 17 years of age with NDO. BOTOX (1 or more of the treatment groups) improves the symptoms of NDO as measured by a reduction from baseline in daytime urinary incontinence episodes.

3 Study Design

This is a multicenter, randomized, double-blind, parallel group study to evaluate the efficacy and safety of BOTOX in patients with urinary incontinence due to NDO who are 5 to 17 years of age. Patients will be evaluated during a screening period for eligibility. Eligible patients will be randomized and receive treatment on day 1. Patients will be centrally randomized and assigned a randomization number prior to treatment in a 1:1:1 ratio to receive a single treatment of 50, 100, or 200 U BOTOX (not to exceed 6 U/kg). Randomization will be stratified by age (< 12 years or ≥ 12 years) and baseline daytime urinary incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day bladder diary collection period). The study medication will be administered via cystoscopy as 20 intradetrusor injections of 0.5 mL each, sparing the trigone.

Patients will have posttreatment follow-up clinic visits at weeks 2, 6, and 12. Thereafter, patients will have alternating telephone and clinic follow-up visits every 6 weeks until they exit the study. Patients exit the study once they qualify for retreatment, or at week 48 if the patient never qualifies for retreatment. Request for retreatment can occur at any scheduled clinic or telephone visit or between scheduled visits from week 12 onwards, and then that clinic visit will also become the qualification for retreatment visit. If the patient qualifies for retreatment they will exit the study, so the visit at which the patient qualifies for retreatment will also become the exit visit. In addition, request for retreatment can occur at a scheduled telephone visit or between scheduled visits after week 12; if this occurs a qualification for retreatment clinic visit should occur within 1 to 2 weeks (which then also becomes the exit visit if the patient qualifies for retreatment).

The primary efficacy measure is daytime urinary incontinence episodes, and the primary timepoint is week 6.

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 102 patients will be randomized at approximately 35 to 45 sites in order to have an estimated 90 patients (30 per treatment group) based on an anticipated dropout rate of 10% by the primary timepoint of week 6.

4.2 Study Population Characteristics

This study will include patients 5 to 17 years of age with urinary incontinence due to NDO who have not been adequately managed with anticholinergics.

4.3 Inclusion Criteria

The following are requirements for entry into the study:

[redacted]

3. male or female, aged ≥ 5 years to ≤ 17 years of age at the time of informed consent

[redacted]

7. patient must be regularly using CIC to empty the bladder [redacted]

[redacted]

[redacted]

4.4 Exclusion Criteria

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

[redacted]

2. patient has had surgery of the spinal cord within 6 months of screening

[redacted]

4. patient has cerebral palsy

[redacted]

8. patient currently uses or plans to use a baclofen pump
9. patient currently uses or plans to use an implantable or nonimplantable electrostimulation/neuromodulation device for treatment of NDO. (If a nonimplantable device is used, it must be discontinued at least 7 days prior to the first screening procedure; if a device is implanted, it must be inactive for at least 4 weeks prior to the first screening procedure; neither should be used during the study).
10. patient uses 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)
11. patient has had previous or current:
    - botulinum toxin therapy of any serotype for any urological condition, or
    - treatment with botulinum toxin of any serotype within 3 months of randomization/day 1 for any other condition or use

[redacted]

[redacted]

19. patient has any medical condition that may put them at increased risk with exposure to BOTOX including diagnosed myasthenia gravis, Eaton-Lambert syndrome, or amyotrophic lateral sclerosis

[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.

Patients who are using anticholinergic medication at baseline should continue to take their anticholinergic medication at the same dose throughout the study (except intravesical anticholinergics which are prohibited within 4 weeks of screening and throughout the study).

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 must 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 must 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.

Patients who were not using anticholinergic medication at baseline should not use anticholinergic medication for the duration of the study. The use of intravesical anticholinergic therapy is prohibited within 4 weeks of the start of screening and throughout the study. The use of other medications or therapies, other than anticholinergics, to treat the symptoms of NDO within 7 days of the start of the screening period procedures and during the study is also prohibited.

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 at least 4 weeks prior to the first screening procedure; if a nonimplantable device is used, it must be discontinued at least 7 days prior to the first screening procedure.

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

The study medication will be packaged and labeled in identically appearing vials and reconstituted by an independent drug reconstitutor (IDR) who is not associated or involved with a study patient's care or study assessments, with the exception of study medication preparation. 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

Patients will be randomized centrally and assigned a randomization number prior to treatment. In addition, patients will be stratified by age (< 12 years or ≥ 12 years) and by the number of daytime urinary incontinence episodes reported at baseline (a total of ≤ 6 or > 6 episodes over the 2-day diary). One randomization number will be assigned to each patient prior to treatment and will be associated with 50, 100, or 200 U BOTOX in a 1:1:1 ratio.

5.5 Method for Assignment to Treatment Groups/Randomization

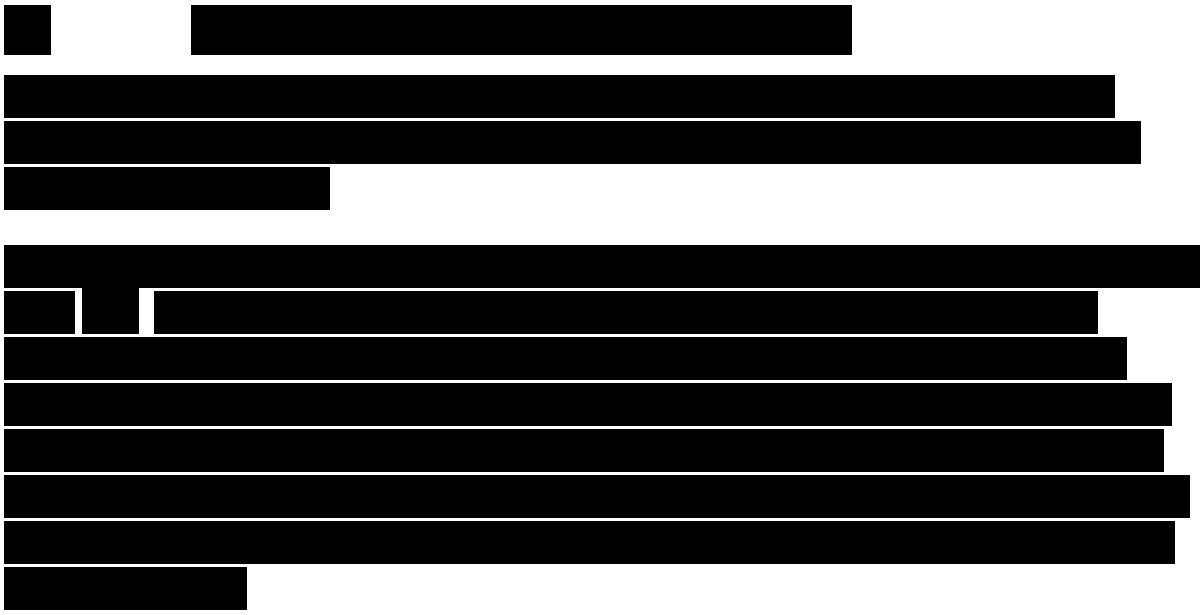
Following the screening period, patients who meet the study inclusion/exclusion criteria and the day of treatment criteria (see Section 5.9.1) will be assigned a randomization number through the interactive voice response system (IVRS)/interactive web response system (IWRS). Study medication will be 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.

5.6 Treatment Regimen and Dosing

All eligible patients enrolled into the study will receive a double-blind treatment of 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).

Treatment will be administered following randomization on day 1 and fulfillment of all the "day of treatment criteria" (see Section 5.9.1). Patients will exit from the study once they

have qualified for retreatment (see Section 5.10.1 for details of qualification for retreatment criteria), and retreatment will be administered in the extension study (191622-121) for those patients who elect and qualify to enroll. If patients do not qualify for retreatment during 48 weeks following randomization/day 1, they will exit from the study; these patients may also enroll into the extension study at this visit.



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. Instructions for the reconstitution and preparation of study medication are 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

The following "day of treatment criteria" must be fulfilled prior to the 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 treatment

5.9.2 Prophylactic Antibiotics

All patients must receive prophylactic antibiotics prior to treatment administration on randomization/day 1.

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).

[redacted]

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 by an appropriately qualified anesthesiologist; 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 by an appropriately qualified anesthesiologist; however the use of neuromuscular blocking agents is not permitted
    - local anesthesia to the bladder wall (with or without sedation) will be via the 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 have been identified (eg, during the screening period or at the time of injection).

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 drug 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 a 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 remain in the study until they qualify for retreatment. Once patients have qualified for retreatment they will exit this study (so the clinic visit where they qualify for retreatment also becomes the exit visit). Patients will have the opportunity to enter the extension study

where the retreatment administration will occur for patients who elect and qualify to enroll. Patients who never qualify for retreatment will exit the study at the week 48 visit, and will also have the opportunity to enter the extension study at this visit.

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 parent/patient/caregiver.

Patients/parents/caregivers can request retreatment at any scheduled clinic visit from week 12 onwards, (ie, at a week 12, 24, 36, or 48 clinic visit), at a scheduled telephone visit (ie, at a week 18, 30, or 42 telephone visit), or between scheduled visits. If the request is made at a scheduled clinic visit and all "qualification for retreatment criteria" are fulfilled, that visit then becomes a qualification for retreatment visit and the additional procedures will be performed. If the request occurs at a scheduled telephone visit or between visits, a qualification for retreatment clinic visit should be conducted within approximately 1 to 2 weeks of the request and the "qualification for retreatment criteria" should be assessed prior to performing any other procedures. The reason for the request will be collected.

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

- Patient/parent/caregiver requests retreatment
- patient has a total of at least 2 daytime urinary incontinence episodes over the 2-day bladder diary collection period
- at least 12 weeks has elapsed since treatment 1
- patient has not experienced a serious treatment-related adverse event at any time

6 Response Measures and Summary of Data Collection Methods

6.1 Efficacy Measures

6.1.1 Primary Efficacy Measure

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

6.1.2 Secondary Efficacy Measures

There are several urodynamic secondary efficacy measures; a central reviewer will determine the final value.

- MCC (mL)
    - the MCC will also be presented as a proportion of the expected bladder capacity (EBC), where EBC is calculated as: (30 + [age in years × 30]) for patients who have volumes below the adult volume of 500 mL (age is at the time of the assessment) (Nevéus et al, 2006)
- presence or absence of an IDC
- if an IDC is present, maximum detrusor pressure during the first IDC ($Pdet_{Max1stIDC}$) (cm H_2O)
- maximum detrusor pressure during the storage phase ($Pdet_{Max}$) (cm H_2O)
- if a leak occurs, detrusor leak point pressure (DLPP) (cm H_2O)
- urine volume at first morning catheterization (mL)
- presence or absence of night time urinary incontinence

In addition, the following duration of effect measures are considered secondary efficacy measures:

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

[redacted]

6.2 Safety Measures

- adverse events
- serious adverse events

[redacted]

6.3 Examination Procedures, Tests, Equipment, and Techniques

Screening procedures can commence once the parental/legal guardian consent, minor assent, and data authorization/protection forms have been obtained; screening will be considered to have started (eg, day -28) at the time of the first screening activity or procedure. On completion of screening, when all the required inclusion/exclusion and "day of treatment criteria" have been met, the patient will be randomized (day 1) and 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).

6.3.2 Medical History

The patient's medical history (all history occurring in the past year and all other relevant history, in the investigator's opinion), including diagnosis or symptom, date of onset, current status, and associated surgical procedures (including name of procedure and date of surgery) will be documented. In addition, the presence or absence of the following baseline

characteristics will be collected: detrusor sphincter dyssynergia, bladder sensation with filling, fecal incontinence, and ambulatory status.

The number of UTIs in the 6 months prior to screening will be documented.

6.3.3 Physical Examination

The physician or appropriately qualified designee will examine the patient for any physical abnormalities of the following body systems at screening and exit: general appearance, HEENT (head, eyes, ears, nose, throat), heart/cardiovascular, lungs, abdomen, neurologic, extremities, back, musculoskeletal, lymphatic, skin, genitourinary, and other findings.

6.3.4 Weight and Height

Weight and height should be measured using a calibrated scale and measuring tape/ruler according to local site practice. Weight or height reported by the patient, parent, or legally authorized representative will not be acceptable.

Weight and height will be measured during the screening period (which for this evaluation can include prior to randomization on day 1) and, if the patient qualifies for retreatment, at the qualification for retreatment clinic visit.

For patients who do not enter the extension study, weight and height will be measured at the exit visit of the current study (191622-120).

6.3.5 Vital Signs

Vital signs will be measured at each study clinic visit prior to any invasive procedures as outlined below. The same procedure used for a patient should be used throughout the study.

Pulse rate (beats per minute): patients should be resting for at least 3 minutes. Pulse rate is then counted over 30 seconds and multiplied by 2.

Blood pressure (mm Hg): the correct size blood pressure cuff for the size of the patient should be used. Patients should be resting for at least 3 minutes. Systolic/diastolic blood pressure is then measured with a sphygmomanometer.

Respiration rate (breaths per minute): patients should be resting for at least 3 minutes. Respiration rate is counted over 30 seconds and multiplied by 2.

Temperature (ºF or ºC): patients should be rested and the body temperature taken according to local site practice (oral, axillary, or tympanic).

Vital signs will be compared to age-appropriate normative values.

6.3.6 Bladder Diary

Patients/parents/caregivers will collect bladder diary data [redacted]. For screening, the bladder diary can be completed [redacted]. The same person(s) (patient or parent(s)/caregiver) should complete the bladder diary throughout the study where possible. For example, if the patient is able to complete the bladder diary themselves during the screening period, they should complete it 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 bladder diary will capture the following information:

- day/date, time, and type (urinary incontinence, catheterization, voluntary void) of each voiding episode during the daytime (time between waking up to start the day and going to bed to sleep for the night)
- volume of urine on catheterization at morning wakening
- time of night sleep and morning wakening
- whether urinary incontinence occurred during the night

More detailed instructions on the patient bladder diary will be provided to the patient and parent/caregiver.

The diary data will be used to satisfy eligibility requirements for study entry, as well as for qualification for retreatment.

6.3.7 Urodynamic Testing

Urodynamic testing will be standardized across all study sites (Attachment 12.3) and performed during the [redacted]

Patient eligibility with regard to the presence of an IDC will be determined by the investigator from either the urodynamics procedure performed during the screening period or from a historical urodynamic evaluation.

Urodynamic data will be reviewed by an independent central reviewer to determine final values for analysis purposes for the parameters listed below. The principal investigator, subinvestigator, or trained technician will perform urodynamic procedures on each patient, then interpret and record the results on the calculation worksheet. A copy of the worksheet, along with the printed tracings will be submitted to the central reviewer. If the central reviewer's interpretation of the results differs from that of the investigator, the central reviewer's results will be used for final analysis. Study sites will not typically be informed of any differences between their urodynamic values and the urodynamic values determined by the central reviewer. However, study sites may receive feedback and/or retraining if data validity is uncertain, if persistent methodological issues arise, or if a data value needs to be rechecked/reconfirmed by the site.

The following urodynamic parameters are to be measured:

- MCC (mL)
- presence or absence of an IDC
- if an IDC is present, $Pdet_{Max1stIDC}$ (cm H_2O)
- $Pdet_{max}$ (cm H_2O) during storage
- if leak occurs, DLPP (cm H_2O)

Refer to Attachment 12.3 for the standardized urodynamic procedure. Related forms will be provided in the Study Procedure Manual.

6.3.8 Bladder and Kidney Ultrasound

Ultrasound of the bladder and kidneys [redacted] For the screening ultrasound only, bladder wall thickness will be determined. For this measurement, the bladder will be filled to ≥ 50 to 90% of the age-expected bladder capacity, or the bladder capacity prior to leakage.

If the patient qualifies for retreatment, an ultrasound of the bladder and kidneys will also be performed at the qualification for retreatment clinic visit. In addition, for patients who do not enter the extension study, a bladder and kidney ultrasound will be performed at the exit visit.

In the case of unclear new findings suggestive of stones (kidney, ureter, or bladder), other diagnostic measures must be performed to confirm the presence of stones (eg, x-ray with or without contrast, urogram, computed tomography scan, magnetic resonance imaging, or cystoscopy). Treatment should not be administered if bladder stones are identified.

[redacted]

6.3.10 Hematology and Clinical Chemistry

A blood sample for hematology and nonfasting clinical chemistry assays by a central laboratory will be taken at the time the IV line is started for general anesthesia on day 1 prior to treatment administration (if no general anesthesia is to be administered a blood sample is taken prior to randomization/treatment). A blood sample will also be taken [redacted].

Analytes will be obtained as specified below, except for the week 12 sample where only complete blood count, blood urea nitrogen (BUN), and creatinine will be obtained:

- hematology: hemoglobin, hematocrit, RBC count, RBC morphology, WBC count, neutrophils, bands, lymphocytes, monocytes, basophils, eosinophils, and platelets

- blood chemistry: glucose, creatinine, BUN, total bilirubin, aspartate aminotransferase/ serum glutamic oxaloacetic transaminase, alanine aminotransferase/serum glutamic pyruvic transaminase, alkaline phosphatase, uric acid, sodium, potassium, bicarbonate (carbon dioxide content), chloride, phosphorus, calcium, magnesium, and total protein

Laboratory results will be compared to age-appropriate normative values.

6.3.11 Renal Function Testing

Renal function will be monitored by Allergan from an estimate of the glomerular filtration rate (eGFR) determined from the serum creatinine levels [redacted]

The calculation of eGFR will be based on the formula of Schwartz and Work (2009) as follows:

$$eGFR = 0.41 \times \text{height (cm)}/\text{serum creatinine (mg/dL)}$$

For eGFR [redacted] the height values used in the calculation will be based on values collected at screening. At study exit, the height values used in the calculation will be based on values collected at exit.

6.3.12 Immunogenicity Testing

Blood samples for immunogenicity testing will be collected [redacted]

Serum samples will be collected and stored [redacted]

A 2-step process will be used for the detection of binding and neutralizing antibodies to BoNT/A. In step 1, serum samples will be screened for reactivity using a validated enzyme-linked immunosorbent assay (ELISA) to determine the presence of toxin-binding antibodies. In step 2, only samples from subjects which were considered positive for toxin-binding antibodies in the ELISA will be tested for neutralizing antibodies to BOTOX. This will be done using a validated mouse protection assay (MPA).

6.3.13 Pregnancy Test

Urine pregnancy testing will be performed during the screening period on females who are postmenarche, [redacted]. A negative result is required prior to receiving study medication.

6.3.14 Health Outcome Measures

The PinQ is completed [redacted] The Modified TBS is completed at [redacted]

Questionnaires should be completed prior to the patient undergoing any procedure for any study visit and prior to study treatment and will completed as detailed 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.

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, urine culture and sensitivity)
- containers to measure volume of urine at first morning catheterization
- patient bladder diaries

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
- flexible or rigid cystoscope with injection port and needles for injection
- all necessary equipment to measure the required urodynamic parameters
- ultrasound for kidney and bladder assessment

- internet connection (high-speed connection) for eCRF completion

6.5 Summary of Methods of Data Collection

An IVRS/IWRS will be used to screen, randomize, and manage the 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. 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 statistical analysis will be conducted when all patients have completed or exited the study. Throughout the entire study, both patients and investigators will remain blinded to treatment. A detailed statistical analysis plan will be finalized prior to the study database lock.

7.1 Analysis Populations

Two different populations will be defined for the statistical analysis: safety and modified intent-to-treat (mITT).

The safety population will include all patients who undergo the treatment procedure and receive study drug on randomization/day 1 and will be analyzed on an as-treated basis

(ie, using the dose actually received with all patients allocated to the nearest dose group [50, 100, or 200 U BOTOX]).

The mITT population will include all randomized patients who received treatment on randomization/day 1 and will be analyzed on an as-randomized basis, except for patients who received less than their randomized dose due to the limit of 6 U/kg, as they will be grouped to the nearest dose group (50, 100, or 200 U BOTOX) based on the dose actually received. Demographics, baseline characteristics, and efficacy variables will be analyzed using the mITT population.

7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

The primary 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 and during the screening period.

In addition, the bladder diary will be used to record the following secondary efficacy assessments:

- urine volume at first morning catheterization (mL)
- presence or absence of night time urinary incontinence

There are several urodynamic secondary efficacy assessments obtained from the urodynamics performed at week 6 and during the screening period; a central reviewer will determine the final value.

- MCC (mL)
- presence or absence of an IDC
- if an IDC is present, $Pdet_{Max1stIDC}$ (cm H_2O)
- $Pdet_{Max}$ (cm H_2O) during storage
- if leak occurs, DLPP (cm H_2O)

Visit windows for the analysis at each timepoint will be defined in the statistical analysis plan.

7.2.1 Primary Efficacy Variable

The primary efficacy variable is the change from baseline posttreatment in the 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, and baseline frequency is defined as the daily average frequency of episodes of daytime urinary incontinence preceding the study treatment. 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 primary timepoint will be week 6 posttreatment.

For the baseline and posttreatment data, a patient must have at least 1 valid diary day (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, then the frequency of daytime urinary incontinence will be considered as missing. Missing frequency of episodes of daytime urinary incontinence at baseline will be imputed using the median of all nonmissing values at baseline within the same treatment group. For the scheduled visits up to week 6 after the study treatment, missing frequencies of episodes of daytime urinary incontinence will be replaced using the last observation carried forward approach. No imputation will be done for missing values on visits after the week 6 visit.

7.2.2 Secondary Efficacy Variables

There are 7 secondary efficacy variables assessed at the week 6 primary timepoint:

- change from baseline in MCC (mL)
- presence or absence of an IDC
- if an IDC is present, change from baseline in $Pdet_{Max1stIDC}$ (cm H_2O)
- change from baseline in $Pdet_{Max}$ (cm H_2O)

- change from baseline in DLPP (cm H_2O)
- change from baseline in average urine volume at first morning catheterization (mL)
- presence or absence on night time urinary incontinence

No imputation will be done for the missing values of the secondary efficacy variables. For the urodynamic secondary variables (MCC, presence/absence of an IDC, $Pdet_{Max1stIDC}$, $Pdet_{Max}$, and DLPP), the values provided by the central reviewer will be used.

The average urine volume at first morning catheterization will be calculated from the values recorded in the bladder diary. Similarly the presence/absence of night time urinary incontinence will be based on the response to the question asked each morning in the diary as to whether the patient had urinary incontinence during the night.

7.3 Hypothesis and Methods of Analysis

All data will be summarized with descriptive statistics and/or frequency tables. Categorical variables will be analyzed using Fisher's exact test, Pearson's chi-squared test, or Cochran-Mantel-Haenszel (CMH) methods, as appropriate. Continuous variables will be analyzed using analysis of variance (ANOVA) or analysis of covariance (ANCOVA), as appropriate. For the evaluation of efficacy analysis described below, a 2-sided test with a p-value ≤ 0.05, unadjusted for multiplicity, will be considered statistically significant, unless specified otherwise.

7.3.1 Primary Efficacy Analyses

The primary efficacy analysis will be based on the mITT population, with imputation of missing values as described in Section 7.2.1. The primary timepoint will be week 6 after treatment.

For each of the BOTOX doses, descriptive statistics will be provided for the daily average frequency of daytime urinary incontinence episodes at baseline and week 6, together with the change from baseline (arithmetic mean and least-squares [LS] mean); the 95% confidence intervals (CI) of the arithmetic and LS mean change will be provided.

For each of the BOTOX doses of 200 U and 100 U, the null hypothesis is that there is no difference between that dose group and the 50 U BOTOX dose group in mean change from baseline in daily average frequency of daytime urinary incontinence episodes at week 6. The alternative hypothesis is that there is a difference in mean change from baseline in daily

average frequency of daytime urinary incontinence episodes between that BOTOX dose group and the 50 U dose group at week 6.

The hypotheses will be tested using an ANCOVA model with baseline value as covariate and treatment group, age (< 12 years or ≥ 12 years), baseline daytime urinary incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day diary collection period), and concurrent anticholinergic therapy (use or nonuse) as factors.

A hierarchical analysis strategy (Lubsen and Kirwan, 2002) will be used to control type I error due to the multiplicity issues related to the primary efficacy analyses for the primary efficacy variable. In the order of (1) 200 U versus 50 U BOTOX, and (2) 100 U versus 50 U BOTOX, treatment group differences will be tested at the 0.05 significance level in a fixed sequence fashion. Results of hypothesis testing for 100 U versus 50 U BOTOX will be considered for statistical significance only if the treatment difference for 200 U versus 50 U BOTOX is shown to be statistically significant.

The treatment difference in mean change from baseline for 200 U versus 50 U BOTOX and 100 U versus 50 U BOTOX will be calculated, as well as the 95% CI of these differences.

The treatment-by-investigator interaction will be assessed.

7.3.2 Secondary Efficacy Analyses

[redacted]

7.3.2.2 Efficacy Analyses for the Secondary Efficacy Variables

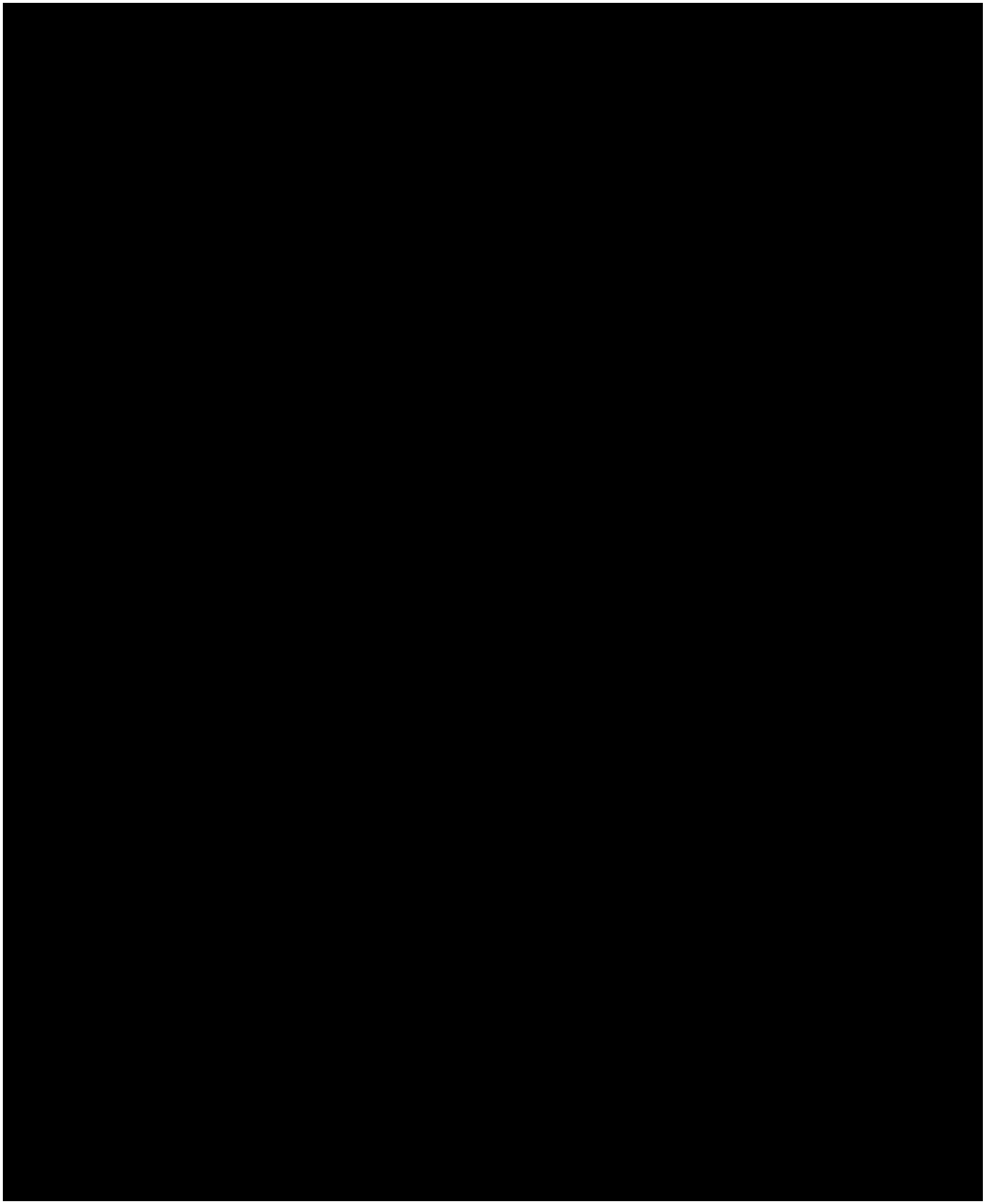
The analysis of MCC, $Pdet_{Max}$, and average urine volume at first morning catheterization at week 6 after treatment will generally be analyzed as described for the primary efficacy endpoint in Section 7.3.1, except that the hierarchal testing strategy will not be implemented. For the urodynamic variables, only the central reviewer's interpretation will be analyzed.

For analysis of MCC, data will also be presented as a proportion of the EBC, where EBC = (30 + [age in years × 30]) for volumes below the adult volume of 500 mL (age is at the time of the assessment).

The proportions of patients with presence/absence of an IDC at week 6 will be presented and analyzed using the CMH method (200 versus 50 U BOTOX and 100 versus 50 U BOTOX) controlling for age (< 12 years or ≥ 12 years), baseline daytime urinary incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day diary collection period), and concurrent anticholinergic therapy (use or non-use).

For the analysis of night time urinary incontinence, the numbers and proportions of patients who experienced night time urinary incontinence on 0, 1, or 2 nights will be presented.

Analysis of time to patient request for retreatment and time to patient qualification for retreatment will be performed as described in Section 7.3.3.4 Duration of Effect.



AUC = area under the curve

[redacted]

[redacted].

7.3.3.4 Duration of Effect

A preliminary estimate of duration of treatment effect will be assessed on completion of this study (on completion of the extension study, a further estimate will be presented using data integrated across both studies). Time from treatment on day 1 to request for retreatment will be estimated using the Kaplan-Meier survival method for each treatment group. 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 during the study and the median duration by days/weeks 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 safety population. Safety variables are adverse events, serious adverse events, [redacted]

[redacted]

[redacted]

7.5 Sensitivity Analysis

Sensitivity analyses of the primary efficacy variable, using both the PP population and the median imputation method for the mITT population will be performed. Missing values will be imputed by using the median of the nonmissing values within the same treatment group at the same timepoint.

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

7.6 Subgroup Analyses

The primary efficacy analysis will be presented by investigator site as well as by key demographic or baseline characteristics, including concurrent anticholinergic therapy (use and nonuse), baseline daytime urinary incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day diary collection period), age (< 12 years or ≥ 12 years), race, and sex.

7.7 Sample Size Calculation

The sample size calculation for this study is determined empirically, while taking into account the treatment effect observed in the adult pivotal phase 3 studies, 191622-515 and 191622-516. The mean (standard deviation) of the change from baseline in daily urinary incontinence at week 6 was -3.1 (3.44) and -3.1 (2.58) in Studies 191622-515 and 191622-516, respectively.

Approximately 34 patients per treatment group are to be enrolled for the study. This includes 30 patients per treatment group and an increase to 34 per group in order to address patient attrition (estimated to be 10% by week 6)

The following table displays estimates of the distance for treatment differences between BOTOX 200 U (maximum 6 U/kg) and 50 U (maximum 6 U/kg) in mean daily average frequency of daytime episodes of urinary incontinence change from baseline at week 6 for a range of common standard deviations (SD). All calculations assume 30 patients per treatment group and a 2-sided test significance level of 0.05. The calculation was performed using the commercial software nQuery Advisor (procedure MTC0-1), version 6.01, and the CI is based on the large sample z statistic.

Standard Deviation	Distance From Mean to the Limit
2.0	1.012
2.5	1.265
3.0	1.518
3.5	1.771
4.0	2.024

Note: The ranges of the SDs are determined based on the values from the adult pivotal phase 3 studies (191622-515 and 191622-516). The estimate of the SD for the 200 U BOTOX treatment group is 3.44 for Study 191622-515, 2.58 for Study 191622-516, and 3.10 for the 2 studies combined.

7.8 Interim Analyses

No interim analysis is planned for this study.

8 Study Visit Schedule and Procedures

Please see Table 1 for a schematic of the schedule of visits and procedures, Figure 1 for the visit flow chart, and Section 6.3 for detailed information on study procedures, tests, equipment, and techniques.

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.

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.

Further information is provided in Section 10.1.

Each patient who provides informed consent and/or assent will be assigned a patient number via IVRS/IWRS that will be used on patient documentation throughout the study.

8.2 Procedures for Final Study Entry

Final study eligibility will be determined at [redacted] to confirm that patient bladder diary records support protocol requirements for urinary incontinence. In addition, prior to randomization, the investigator should confirm that the day of treatment criteria have been fulfilled (Section 5.9.1). Patients should continue to meet other inclusion and exclusion criteria as specified in Sections 4.3 and 4.4 of the protocol.

A patient is considered to have entered the study when they are randomized to treatment.

See Section 5.5 for the method for assignment to treatment groups/randomization.

8.3 Visits and Associated Procedures

For a summary of the procedures to be performed, [redacted] A description of individual procedures is provided in Section 6.3. The total number of clinic visits and study duration for each patient will depend on whether patients request and qualify for retreatment. Evaluations should be performed by the same evaluator throughout the study whenever possible. [redacted]

8.4 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

8.5 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.

8.6 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 (nonstudy procedures), and their compliance with the protocol since the previous visit.

8.7 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.

8.8 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

8.9 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.

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. In addition, during the screening period, adverse events will be assessed regardless of the administration of a pharmaceutical 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.

[redacted]

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 nonspontaneous) 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

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 enrollment into the study, 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 (European sites only), or other country and local patient privacy required documentation for this study has been obtained (including the date)
- date that the patient was randomized into the study, patient number, patient medication kit number, and date and details of study drug administration
- study title and/or the protocol number of the study and the name of Allergan
- dates of all patient visits and date of any request for retreatment

- 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
- 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]
- [redacted]

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

[redacted]

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, [redacted] will be analyzed at a centralized clinical laboratory with certification from a recognized accreditation agency (eg, College of American Pathology [CAP] or Clinical Laboratory Improvement Amendments [CLIA] 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

Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Neurourology and Urodynamics. 2002;21:167-178.

Apostolidis A, Popat R, Yiangou Y, Cockayne D, Ford AP, Davis JB, et al. Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. J Urol. 2005;174:977-983.

Apostolidis A, Dasgupta P, Fowler CJ. Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. Eur Urol. 2006;49:644-650.

Bachmann C, Lehr D, Janhsen E, Steuber C, Gäbel E, von Gontard A, et al. German version of the pediatric incontinence questionnaire for urinary incontinence health related quality of life. J Urol. 2009;182:1993-1999.

Bauer SB, Hallet M, Khoshbin S, Lebowitz RL, Winston KR, Gibson S et al. The predictive value of urodynamic evaluation in newborns with myelodysplasia. JAMA. 1984;152: 650-652.

Bower WF, Sit FKY, Bluyssen N, Wong EMC, Yeung CK. PinQ: A valid, reliable and reproducible quality-of-life measure in children with bladder dysfunction. J Pediatr Urol. 2006;2:185-189.

Chancellor MB, Fowler CJ, Apostolidis A, de Groat WC, Smith CP, Somogyi GT, et al. Drug insight: biological effects of botulinum toxin A in the lower urinary tract. Nat Clin Pract Urol. 2008:5(6);319-328.

Coelho A, Dinis P, Ointo R, Gorgal T, Silva C, Silva A, et al. Distribution of the high-affinity binding site and intracellular target of botulinum toxin type A in the human bladder. Eur Urol. 2010:57;884-890.

Colman S, Chapple C, Nitti V, Haag-Molkenteller C, Hastedt C, Massow U. Validation of treatment benefit scale for assessing subjective outcomes in treatment of overactive bladder. Urology. 2008;72(4):803-807.

Cruz F, Herschorn S, Aliotta P, Brin M, Thompson C, Lam W, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2011;60(4): 742-750.

Gamé X, Mouracade P, Chartier-Kastler E, Viehweger E, Moog R, Amarenco G, et al. Botulinum toxin-A (Botox®) intradetrusor injections in children with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic review. J Pediatr Urol. 2009;5:156-164.

Gerridzen RG, Thijssen AM, Dehoux E. Risk factors for upper tract deterioration in chronic spinal cord injury patients. J Urol. 1992;147:416-418.

Ginsberg D, Gousse A, Keppenne V, Sievert KD, Thompson C, Lam W, et al. Phase 3 efficacy and tolerability study of onabotulinumtoxinA in patients with urinary incontinence resulting from neurogenic detrusor overactivity. J Urol. 2012;187:2131-2139.

Joseph DB, Bauer SB, Colodny AH, Mandell J, Retik AB. Clean intermittent catheterization of infants with neurogenic bladder. Pediatrics. 1989;84(1):78-82.

Lubsen J and Kirwan B-A. Combined endpoints: can we use them? Statistics in Medicine. 2002;21(19):2959–2970.

McGuire EJ, Woodside JR, Borden TA, Weiss RM. Prognostic value of urodynamic testing in myelodysplastic patients. J Urol. 1981;126(2):205-209.

Nevéus T, von Gontard A, Hoebeke P, Hjälmås K, Bauer S, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the standardisation committee of the international children's continence society. J Urol. 2006;176:314-324.

Sager C, Burek C, Durán V, Corbetta JP, Weller S, Bortagaray J, et al. Pharmacotherapy in pediatric neurogenic bladder intravesical botulinum toxin type A. ISRN Urology. 2012; 2012:article ID 763159, 6 pages.

Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol. 2009;4:1832-1843.

Tekgül S, Riedmiller H, Dogan HS, Gerharz E, Hoebeke P, Kocvara R, et al. Guidelines on pediatric urology. Uroweb 2012. Available at http://www.uroweb.org/gls/pdf/21_Paediatric_Urology_LR_August%202012.pdf. Accessed January 14, 2013.

van Gool JD, Dik P, de Jong TPVM. Bladder-sphincter dysfunction in myelomeningocele. Eur J Pediatr. 2001;160:414-420.

12 Attachments

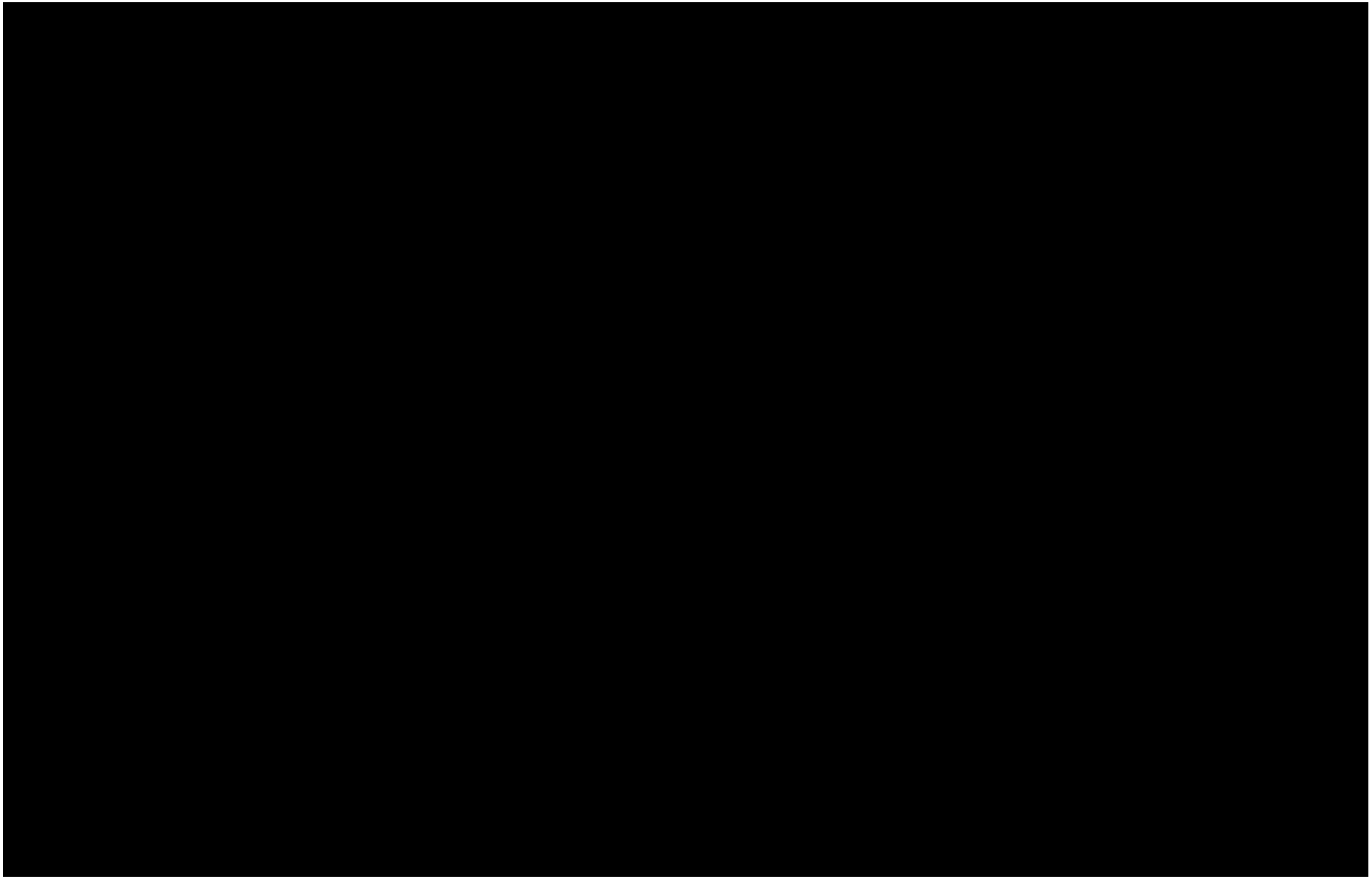
12.1 Preparation of Study Medication

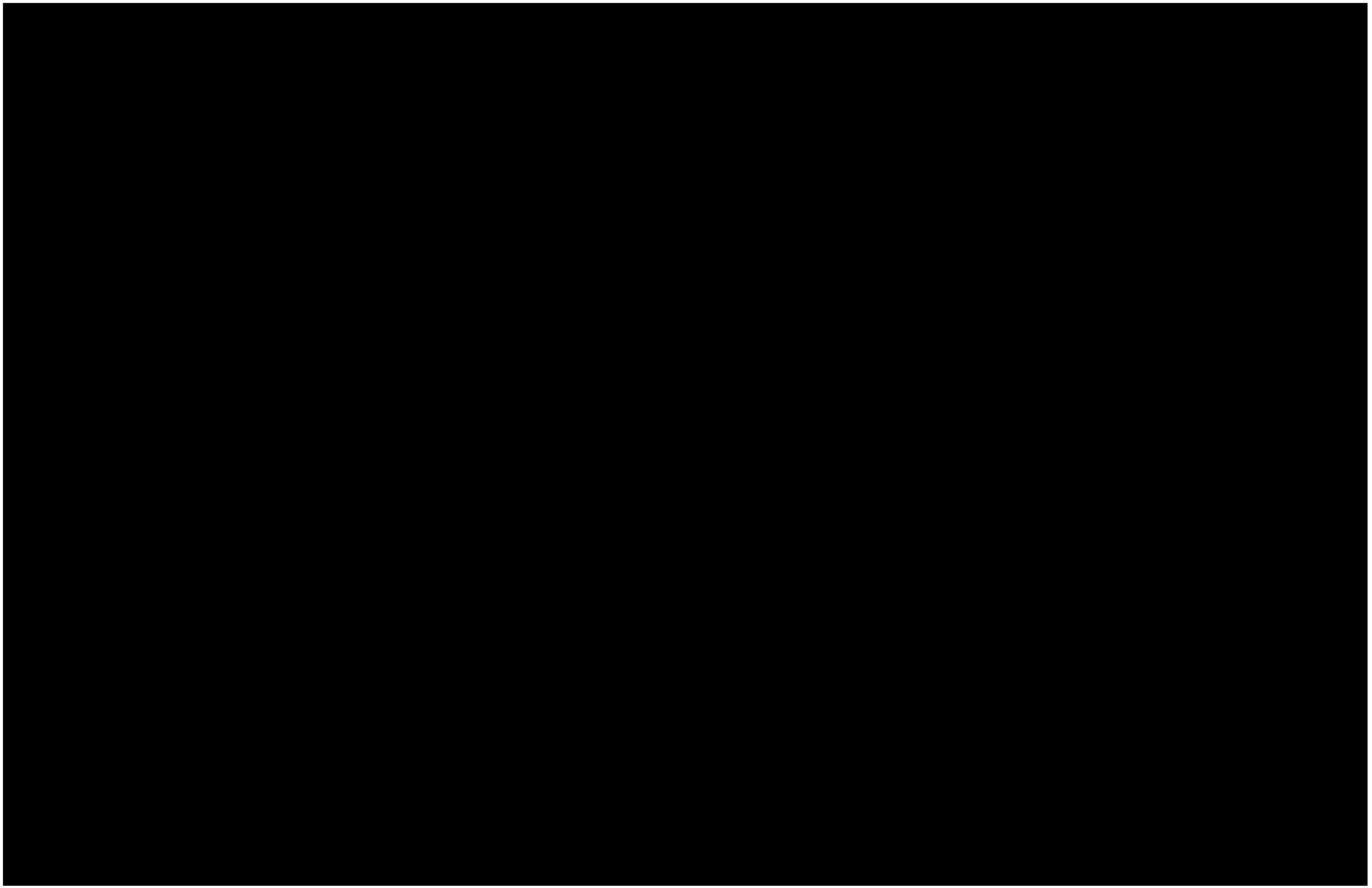
Study medication vials will be reconstituted for the 50, 100, and 200 U BOTOX dose groups (not to exceed 6 U/kg) based on the tables in the following sections.

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.

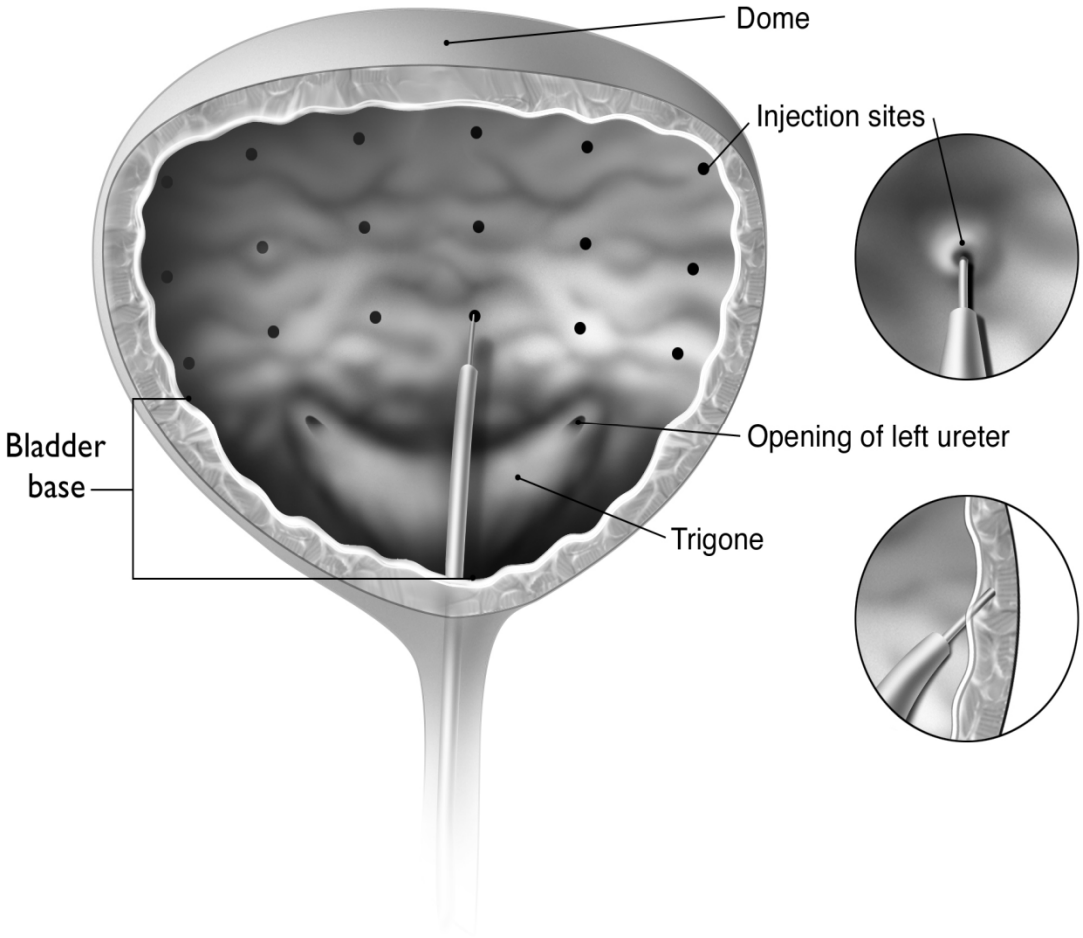
Once the diluent has been drawn into the vial, the vial should be rotated gently to mix the contents. The reconstituted study medication should be clear, colorless and free of particulate matter.

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 the 191622-120 Pharmacy Manual.





12.2 Study Treatment Injection Pattern



12.3 Urodynamic Procedure

12.3.1 Overview

Urodynamic testing will be standardized across all participating study centers and consequently artifacts inherent in the procedure are minimized. Urodynamics must be performed by the principal investigator, subinvestigator, or a trained technician, qualified to perform the procedure (ie, experienced in performing pressure/flow cystometry).

The principal investigator, subinvestigator, or trained technician will perform the urodynamic procedure, then interpret and record the results on the calculation worksheet. The worksheet should be completed to derive the values which are provided to the central reviewer. The worksheet and the tracings must be signed and dated by the investigator or physician subinvestigator.

12.3.2 Central Reviewer Process

A copy of the worksheet, along with the printed tracings will be submitted to the independent central reviewer. The independent central reviewer will verify the results provided on the calculation worksheet. If the central reviewer's interpretation of the results differs from that received from the site, the central reviewer's result will be used for final analysis. Study sites will not be informed of any discrepancy between their determinations and the central reviewer's determination. However, study sites may receive feedback and/or retraining if data validity is uncertain or if persistent methodological issues arise.

12.3.3 Site Urodynamic Qualification

To demonstrate that the urodynamic equipment and study site personnel are able to complete the urodynamic testing for central review as specified for this protocol, the tracing should be from a pediatric patient in a comparable age group (ie, 4 to 18 years old), using a tracing/graph showing detrusor overactivity and using the same annotation procedure as defined in this protocol. This qualification tracing may be a tracing that the site has on file (after appropriate release has been obtained, if applicable, per local site practice) or may be a newly produced tracing, and should have anonymized patient identifiers. The qualification tracing must be annotated [redacted] In addition, an event summary, a completed calculation worksheet, and a transmittal form must be submitted with the sample tracing. The central reviewer and Allergan will work with the sites to ensure the sample tracing is acceptable, and that applicable site personnel have received protocol-specific urodynamic training prior to the site being permitted to enroll

patients in the study. Following approval of the sample tracing, subsequent urodynamic studies for this protocol must be performed in the same manner, using the same urodynamic equipment, and the submitted tracing should contain the same data points and annotations as the sample tracing (as applicable). All efforts should be made for the same person to perform the urodynamics testing at a given site.

If new urodynamics equipment is obtained and is intended to be used in this study a new site urodynamic qualification may need to be performed.

[redacted]

12.3.5 Urodynamic Annotations

All urodynamic parameters collected during pressure/flow cystometry must be annotated on the urodynamic tracing electronically so that the tracing is interpretable retrospectively by the independent central reviewer. To ease interpretation, abbreviations should be standardized using the annotations below:

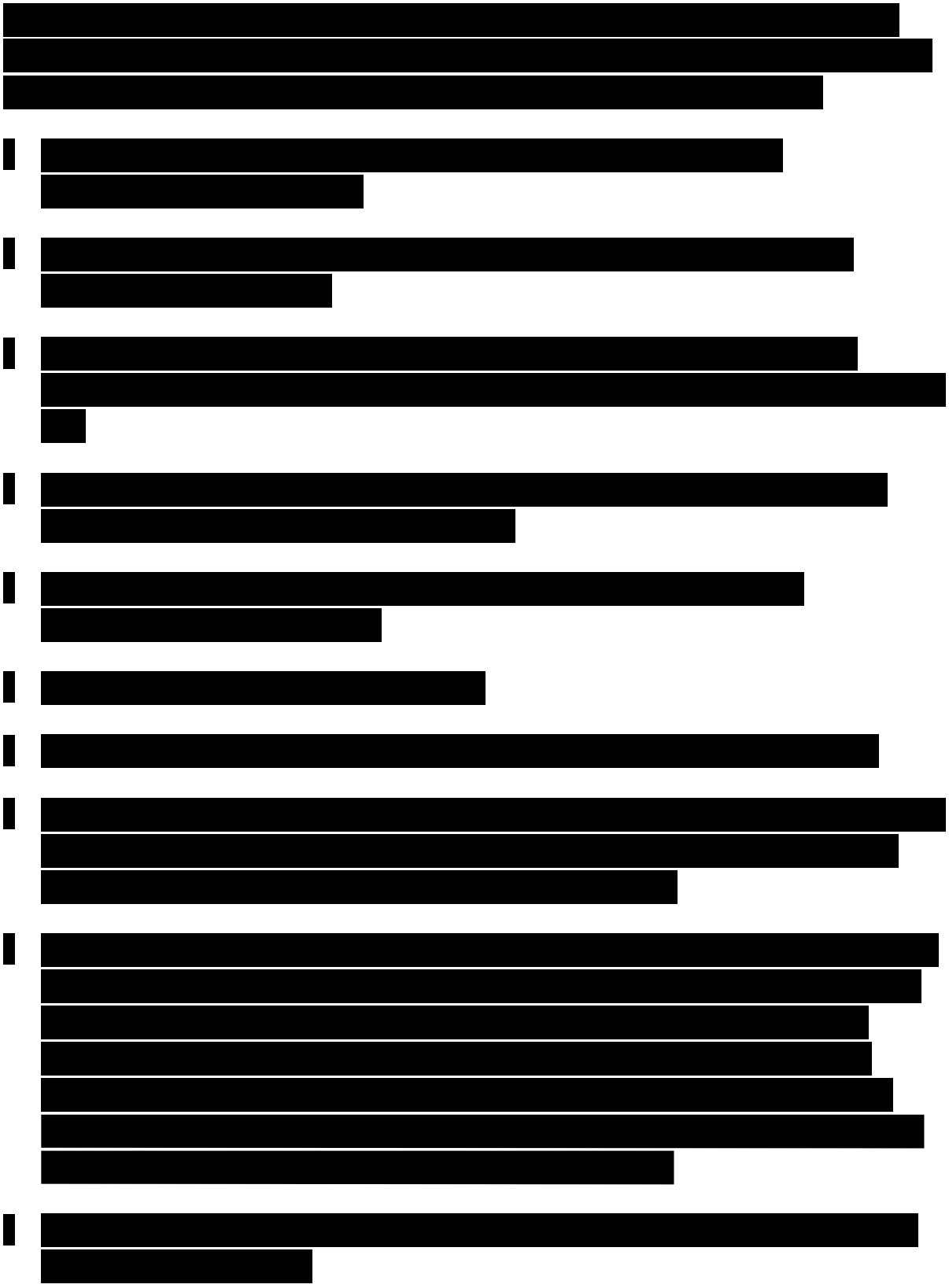
Parameter	Defined As:	Standardized Tracing Annotation
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Maximum cystometric capacity	Point when one of the following criteria is fulfilled: • First leakage is observed NOTE: o Annotate "MCC-IDC Leak" if occurs with an IDC o Annotate "MCC-DLPP" if occurs without an IDC • Patient indicates they can no longer delay micturition because of a strong desire to void, and is given the permission to void, OR patient indicates that they are too uncomfortable to continue the procedure (due to bladder filling) o NOTE: The MCC will be considered to be the point at which the patient enters the voiding phase and is given permission to void. It is also important to clearly annotate whether the void was volitional (voluntary void "VV") • Precipitant void (terminal detrusor overactivity) is observed o NOTE: If the patient has precipitant micturition ie, is about to leak (terminal detrusor overactivity), the MCC should be annotated at the start of the terminal contraction (this may need to be annotated retrospectively). • 500 mL has been instilled into the bladder OR Infused volume is > 150% of expected bladder capacity (EBC), where EBC = (30 + [age in years × 30]) for volumes below the adult volume of 500 mL • In the opinion of the investigator, the patient's safety is possibly compromised with further bladder filling (e.g., elevated bladder pressures, etc)	MCC or MCC-IDC Leak, as applicable

Parameter	Defined As:	Standardized Tracing Annotation
[redacted]	[redacted]	[redacted]
Maximum detrusor pressure during storage phase	Point at which the maximum detrusor pressure in the Pdet channel is observed during the storage phase (eg, the greater of the amplitude of the strongest IDC, the terminal detrusor contraction, the pressure at the end of filling, or the highest pressure at any other time during the storage phase). o NOTE: If leakage occurs at $Pdet_{Max}$ then this is MCC as well	$Pdet_{Max}$
Detrusor Leak Point Pressure	The lowest detrusor pressure at which urine leakage occurs (if present) in the absence of either a detrusor contraction or increased abdominal pressure	DLPP
[redacted]	[redacted]	[redacted]

[redacted]

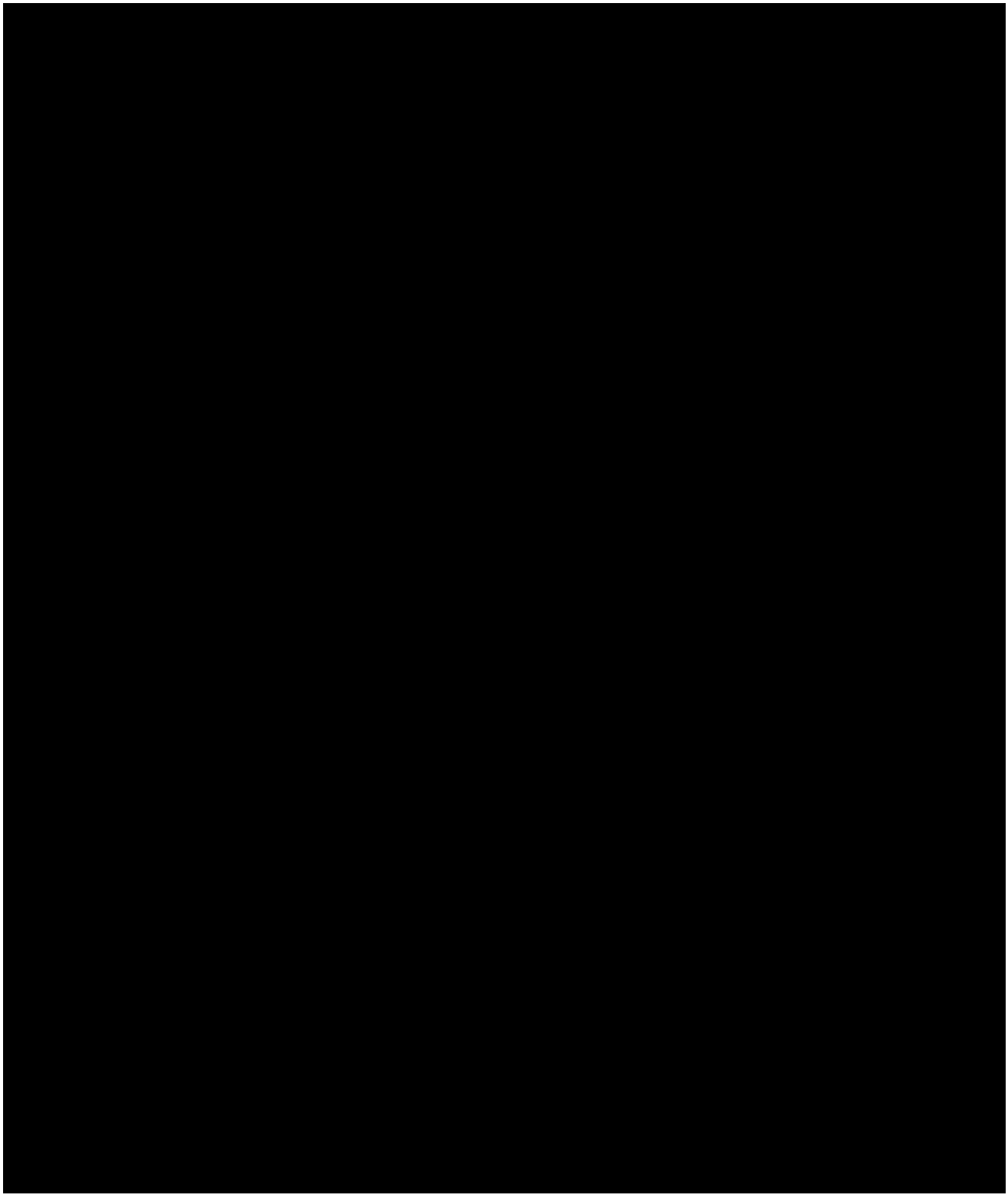
12.3.7 Urodynamic Procedure

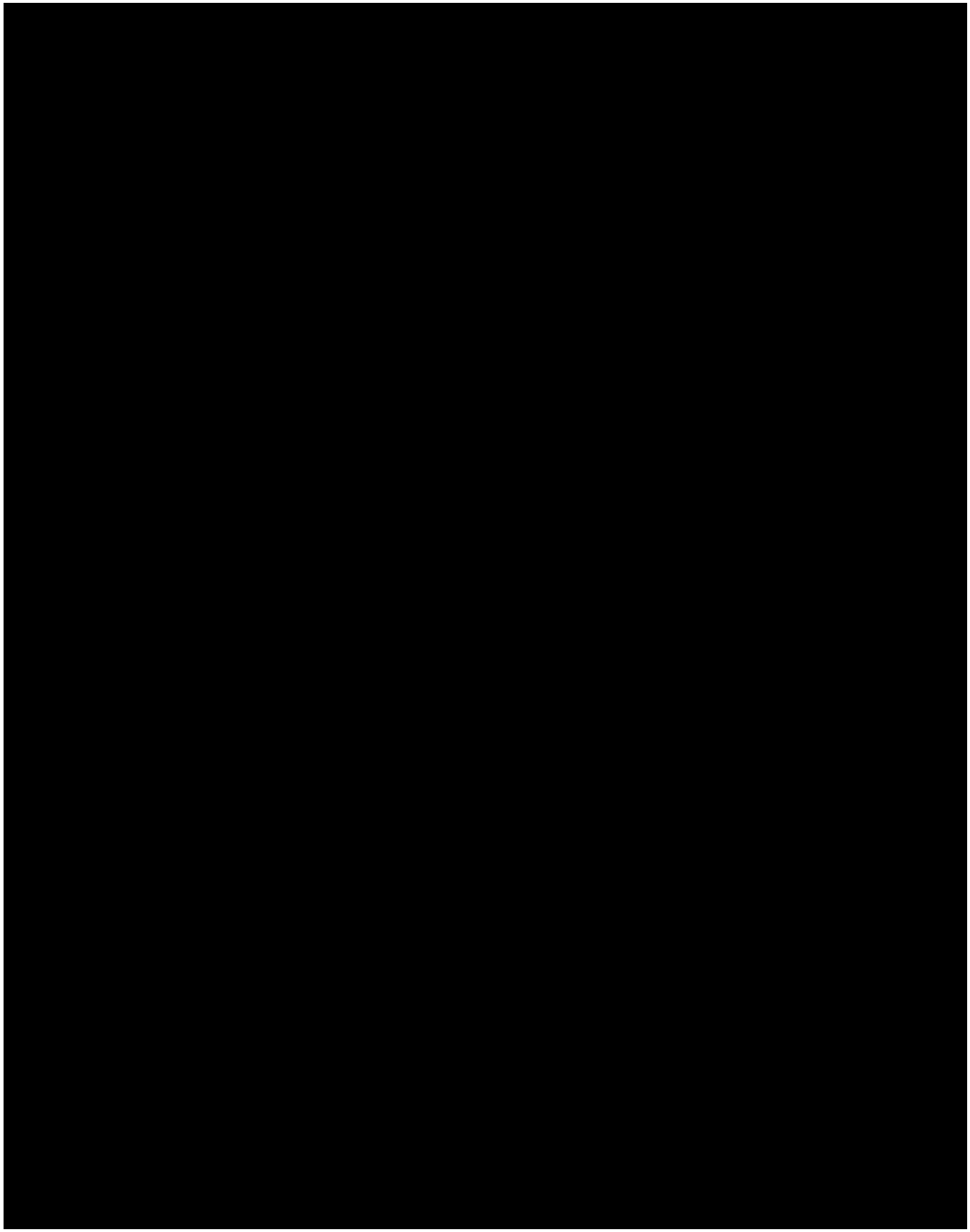
The procedure should be performed in accordance with the investigator's usual practice and available equipment, while complying with the protocol requirements for the procedure and tracing.

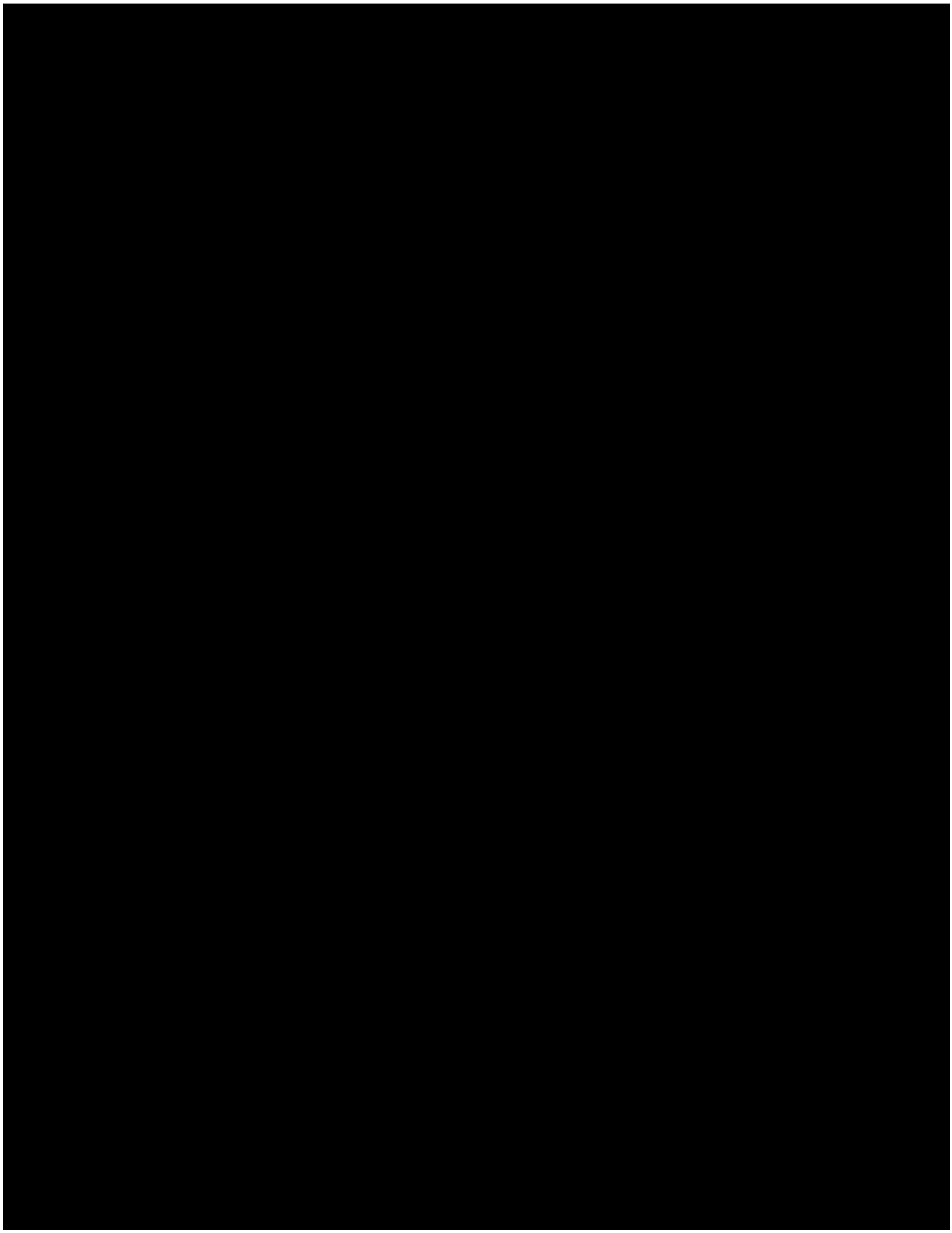


[redacted]

[redacted]







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
$Pdet_{Max1stIDC}$	maximum detrusor pressure during the first IDC
$Pdet_{Max}$	maximum detrusor pressure during the storage phase
PinQ	Pediatric Incontinence Questionnaire
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: BOTOX® in the Treatment of Urinary Incontinence Due to Neurogenic Detrusor Overactivity in Patients 8 to 17 Years of Age

Protocol 191622-120 Amendment 1

Date of Amendment: October 2013

Amendment Summary

This summary includes changes made to Protocol 191622-120 (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 indicating that the Investigator will ensure all participating personnel are adequately informed about the protocol Removed provision for multiple investigator signatures	Global change to Allergan's protocol template
[redacted]	[redacted]	[redacted]

Section	Revision	Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	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 night time incontinence, indwelling catheters will not be allowed during diary collection periods.
[redacted]	[redacted]	[redacted]
Study Schedule (Table 1)/6.3.8 Bladder and Kidney Ultrasound	Added requirement to measure bladder wall thickness by ultrasound at the screening visit	Patients may have urinary bladder fibrosis which is linked with poor compliance. Measurement of bladder wall thickness will allow for further characterization of the patient population being studied.

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
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.
6.3.2 Medical History	Clarified what relevant medical history should be collected and added a sentence to include the collection of the presence or absence of selected baseline characteristics	This provides guidance for sites, and the collection of baseline characteristics will allow further characterization of the patient population being studied.
6.3.4 Weight and Height	Amended text to clarify when height and weight should be measured	Clarifications provided to ensure that data are available when needed for certain calculations, eg, dose based on patient weight, estimate of glomerular filtration rate
6.3.8 Bladder and Kidney Ultrasound	Amended text to clarify when ultrasound is to be performed	Clarification
6.3.11 Renal Function Testing	New section	Renal function assessment (estimated glomerular filtration rate based on serum creatinine levels and patient height) was added based on Regulatory Agency feedback.
7.4 Safety Analysis	Addition of renal function assessment	Renal function, as assessed by estimated glomerular filtration rate, is now a safety parameter.
8.7 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
10.3.1 Patient Privacy and 10.4.2 Case Report Form Completion	Amended wording	To reflect global change to Allergan's protocol template

Section	Revision	Rationale
12.1.1 BOTOX 50 U 12.1.2 BOTOX 100 U 12.1.3 BOTOX 200 U	Amended lower body weight range from 15 kg (33 lbs) to 14 kg (31 lbs)	Typographical error in original protocol
12.3.3 Site Urodynamic Qualification	Added clarification that the sample urodynamic tracing can be from a urodynamic assessment of a pediatric patient who is comparable in age to the age group of study participants and that traces will be anonymized	To clarify sample tracing procedures and comply with patient privacy laws
12.3.5 Urodynamic Annotation	Added that first leakage can occur with or without an IDC and annotations should be reflected accordingly	Clarification
12.3.8 Parameters to be recorded on the worksheet	Added volume at first IDC	Additional measurement required for calculation worksheet
12.5 Package Insert	Removed section	Global change to Allergan's protocol template

12.7 Protocol Amendment 2 Summary

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

Protocol 191622-120 Amendment 2

Date of Amendment: April 2016

Amendment Summary

This summary includes changes made to Protocol 191622-120 (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
Section 12.1	Updated dosing table to add row for lower body weight	To include dosing information for a younger patient population.

12.8 Protocol Amendment 3 Summary

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

Protocol 191622-120 Amendment 3

Date of Amendment: September 2017

Amendment Summary

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.

Sections	Revision	Rationale
Synopsis Section 4.4: Number of Patients Section 7.7: Sample Size Calculation	Decreased the sample size from N=132 to N=102	Due to enrollment challenges, the sample size was recalculated. While the revised sample size will provide a wider confidence interval than the current sample size, the proposed reduction should not negatively affect the clinical and scientific integrity of the study. The FDA has concurred with this plan.
Section 7.1: Analysis Populations	Deleted Per-protocol population	To reflect current company standard for not performing analyses on per-protocol population for superiority trials.

ALLERGAN

Protocol 191622-120 Amendment 3

[redacted]

Approval Date: 27-Sep-2017