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STUDY TITLE

BOTOX® in the Treatment of Urinary Incontinence Due to Overactive Bladder in Patients 12 to 17 Years of Age

Protocol Number:	191622-137 Amendment 2
EudraCT Number:	2014-000464-17
Phase:	3
Name of Investigational Product:	BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex (US Adopted Name is OnabotulinumtoxinA)
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Approval Date: 05-Sep-2014

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

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

I agree to:

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

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

Investigator Printed Name	Signature	Date

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Protocol Summary

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

Phase: 3

Study Objectives: To evaluate the safety and efficacy of BOTOX for the treatment of urinary incontinence due to overactive bladder (OAB) in patients 12 to 17 years of age who have not been adequately managed with anticholinergic therapy. To evaluate the safety and efficacy of repeated BOTOX treatments in this patient population.

Clinical Hypotheses: BOTOX (1 or more of the treatment groups) has an acceptable safety profile when injected into the detrusor of patients 12 to 17 years of age with OAB. BOTOX (1 or more of the treatment groups) improves the symptoms of OAB as measured by a reduction from baseline in daytime urinary incontinence episodes.

Study Design

Structure: Multicenter, randomized, double-blind, parallel-group, multiple-dose study

Duration: Patients will participate in the study for at least 96 weeks following entry into the study and should have at least 12 weeks follow-up since the last treatment prior to exiting the study. The minimum duration is therefore 96 weeks, and the maximum duration is approximately 108 weeks (for patients who received their last treatment at week 96 with 12 weeks posttreatment follow-up).

Study Treatment Groups: Eligible patients will be initially allocated to 1 of 3 treatment groups:

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

In order that an upper dosing limit of 6 U/kg is not exceeded, the actual dose administered will be adjusted based on patient weight if necessary.

At each retreatment, the investigator can elect to keep the dose the same or increase the dose one level; if it is deemed that a dose reduction would be warranted then the patient should be exited from the study (see Section 5.5 for further details). The dose decision will be based on the response to the previous treatment. Both the preceding and subsequent dose will remain blinded until the primary analysis has been reported (see Section 7). The dosing options will depend on the investigator's decision as summarized below:

- investigator may elect to keep the same dose as received at the previous treatment (dose not to exceed 6 U/kg)
- investigator may elect to increase the dose compared with the previous treatment (dose not to exceed 6 U/kg) as follows:
    - if the patient received 25 U at the previous treatment, they would receive 50 U
    - if the patient received 50 U at the previous treatment, they would receive 100 U
    - if the patient received 100 U at the previous treatment, they would remain at 100 U

However, for any patient who is already on the highest dose (100 U), if a dose escalation is requested by the investigator on 2 occasions, the patient will be exited from the study upon the second escalation request without receiving any further treatments. In addition, if the investigator assesses that the patient should not be retreated with the current dose and that a dose reduction would be warranted, the patient should be exited from the study as a reduction of dose in this study is not an option. In such cases, the patient will be followed up for a minimum of 12 weeks since their last treatment.

Controls: None

Dosage/Dose Regimen: Multiple treatments may be administered in this study (between 1 and 8 treatments at 25 U, 50 U, or 100 U BOTOX). The first treatment will be administered on day 1 once all "day of treatment criteria" are fulfilled (see Section 5.9.1).

Request for retreatment can occur at scheduled clinic visits, scheduled telephone visits, or between scheduled visits. If the request is made at a scheduled clinic visit, then that visit will also become the qualification for retreatment visit, otherwise a qualification for retreatment clinic visit should be conducted within approximately 1 to 2 weeks of the patient/parent/legally authorized representative request.

The qualification for retreatment criteria are:

- patient/parent/legally authorized representative requests retreatment
- patient has at least 1 daytime urinary urgency incontinence episode over the 2-day diary collection period
- PVR urine volume must be < 200 mL
- at least 12 weeks have elapsed since the patient's previous study treatment
- patient has not experienced a serious treatment-related adverse event at any time

Treatment will be administered within 4 weeks (28 days) after a patient qualifies for retreatment. Retreatment(s) can be administered up to 96 weeks from randomization on day 1 and will only occur 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 can be under local anesthesia (with or without sedation), or general anesthesia.

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

- 25 U BOTOX (not to exceed 6 U/kg)
- 50 U BOTOX (not to exceed 6 U/kg)
- 100 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 baseline daytime urinary urgency incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day diary collection period).

Doses received at subsequent retreatments will be determined by the investigator and will be based upon the patient's response to their previous treatment.

Visit Schedule: Patients will be evaluated during a screening period for eligibility. Eligible patients will be randomized and receive treatment on day 1. All patients will be evaluated at scheduled clinic visits at weeks 2, 6, and 12 posttreatment, and thereafter at alternating telephone and clinic visits every 6 weeks until the patient qualifies for further retreatment or exits the study. Patients can request retreatment from week 12 since the previous study treatment at scheduled clinic visits, telephone visits, or between scheduled visits. If the request is made at a scheduled clinic visit then this also becomes the qualification for retreatment visit, otherwise a qualification for retreatment clinic visit should be conducted within approximately 1 to 2 weeks of the patient/parent/legally authorized representative request. Once qualified for retreatment, the same visit schedule will be followed as described above for the first retreatment. Patients exit once 96 weeks from entry into the study at day 1 has occurred, and at least 12 weeks follow-up since their last treatment has occurred (eg, if a patient receives retreatment at week 96, he/she would exit 108 weeks after day 1).

Study Population Characteristics

Number of Patients: Approximately 108 patients will be randomized at approximately 35 to 45 sites (32 patients per treatment group plus 10% dropout by the primary timepoint of week 12).

Condition/Disease: Urinary incontinence due to OAB

Key Inclusion Criteria:

- male or female, aged ≥ 12 years to ≤ 17 years of age at the time of informed consent
- patient has symptoms of OAB (frequency and urgency) with urinary incontinence for a period of at least 6 months immediately prior to screening, determined by patient history
- patient experiences a total of ≥ 2 episodes of daytime urinary urgency incontinence in the 2-day patient bladder diary completed during the screening period (daytime is defined as time between waking up to start the day and going to bed to sleep for the night)
- patient experiences urinary frequency, defined as an average of ≥ 8 micturitions (toilet voids) per day, ie, a total of ≥ 16 micturitions in the 2-day patient bladder diary completed during the screening period
- patient has not been adequately managed with 1 or more anticholinergic agents for the treatment of OAB in the opinion of the investigator. This includes patients who are still incontinent despite anticholinergic therapy, experiencing intolerable side effects, or are unwilling to continue to take the medication for any reason
- patient is willing and able to use clean intermittent catheterization (CIC) to empty the bladder at any time after study treatment if it is determined to be necessary by the investigator
- patient agrees to a minimum fluid intake of 1500 mL/m^2 body surface area (BSA) per day, not to exceed 3000 mL/m^2 BSA per day, during the patient bladder diary completion days at screening and prior to clinic visits during the study
- negative urine pregnancy test for females who are postmenarche

Key Exclusion Criteria:

- patient has an uncontrolled systemic disease, previous or current diagnosis of malignancy
- patient has symptoms of OAB due to any known neurological reason (eg, spina bifida, spinal cord injury, or cerebral palsy)
- patient has a history of 2 or more urinary tract infections (UTIs) treated with antibiotics within 6 months of randomization/day 1 or is taking prophylactic antibiotics to prevent chronic UTI
- patient has a history or evidence of any pelvic or urological abnormalities, except OAB, including:
    - bladder neck surgery resulting in an open bladder neck, or reconstructive surgery of the lower urinary tract (eg, urostomy, urinary diversion, or bladder augmentation)
    - anatomical evidence of bladder outlet obstruction (including functional outlet obstruction), urethral or urethral valve obstruction/stricture at screening
    - surgery of the urinary tract (including minimally invasive surgery) within 6 months of screening (except those listed above which are exclusionary for any time period)
    - circumcision within 1 month of screening
    - clinically relevant kidney abnormality, or clinically relevant vesicoureteric reflux, or disease of the bladder (other than OAB) that may affect bladder function
- patient has predominance of stress incontinence, or "giggle" incontinence, or any condition other than OAB that in the investigator's opinion may account for the patient being incontinent
- patient has unmanaged, unresolved bowel problems (eg, constipation, encopresis)

- patient currently uses or plans to use medications or therapies to treat symptoms of OAB, including nocturnal enuresis or nocturia. Patients previously receiving these medications must have discontinued their use prior to the start of the first screening procedures as follows:
    - for desmopressin, at least one day prior
    - for anticholinergic therapy, at least 7 days prior
    - for intravesical anticholinergic therapy, at least 4 weeks prior
    - for mirabegron, at least 14 days prior
- patient currently uses or plans to use an implantable or nonimplantable electrostimulation/neuromodulation device for treatment of OAB. (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 CIC or an indwelling catheter to manage their OAB
- 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
- patient has been treated with intravesical capsaicin or resiniferatoxin within 12 months of screening
- patient has a post-void residual (PVR) urine volume of > 40 mL at screening. The PVR measurement can be repeated once on the same day; the patient is to be excluded if the repeated measure is above 40 mL.
- patient has a daytime (waking hours) total volume of urine voided > 3000 mL, collected over one daytime period during the 2-day bladder diary collection period prior to randomization/day 1
- postmenarche female patients of childbearing potential who are pregnant, nursing, or planning to become pregnant during the study (postmenarche female patients must also either be sexually abstinent or use another acceptable form of contraception – see Section 4.5.1.1)
- patient has known allergy or sensitivity to components of any botulinum toxin preparation (including the study medication preparation), anesthetics or antibiotics to be used during the study
- patient has hemophilia, or other clotting factor deficiencies, or disorders that cause bleeding diathesis
- patient cannot withhold any antiplatelet, anticoagulant therapy, or other medications with anticoagulant effects for 3 days prior to randomization/day 1. Note: some medications may need to be withheld for > 3 days, per clinical judgment of the investigator (see Section 4.5.2, Prohibited Medications/Treatments for additional details)
- 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
- patient has a condition or is in a situation that in the investigator's opinion may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study

Response Measures

Efficacy:

Primary:

- number of daytime urinary incontinence episodes

Secondary:

- number of daytime micturition episodes
- number of daytime urgency episodes

- presence or absence of night time urinary incontinence
- volume voided per micturition

Health Outcomes:

- Pediatric Incontinence Questionnaire (PinQ)
- modified Treatment Benefit Scale (TBS)

Safety:

- adverse events
- serious adverse events
- physical examination
- vital signs (pulse rate, blood pressure, respiration rate, and body temperature)
- urine dipstick reagent strip test
- urinalysis (with urine culture/sensitivity, as applicable)
- hematology and clinical chemistry
- PVR urine
- immunogenicity testing
- kidney and bladder ultrasound
- urine pregnancy test for females who are postmenarche
- concomitant medications
- concurrent procedures

General Statistical Methods and Types of Analyses:

The BOTOX-treated population will be used for the efficacy and safety analyses. Patients who are enrolled and receive at least 1 BOTOX treatment on randomization/day 1 will be included in the BOTOX-treated population. A primary analysis will be conducted when all BOTOX-treated patients have either: 1) qualified for retreatment, 2) completed 48 weeks since randomization on day 1, or 3) prematurely exited prior to 48 weeks, whichever occurs sooner. The primary analysis will include all data available at the time the last patient fulfills the above requirement, with the primary timepoint being week 12 of treatment cycle 1; data on duration of effect for treatment cycle 1 will also be analyzed. In addition, data from patients that received more than 1 treatment will also be analyzed. The final analysis will be performed on study completion.

The primary efficacy variable is the change from study baseline at week 12 posttreatment 1 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. The daily average frequency of daytime urinary incontinence episodes will be normalized to a 12-hour daytime period (daytime is defined as the time between waking up to start the day and going to bed to sleep for the night). For patients who receive multiple treatments, week 12 after each treatment will be the timepoint of main interest. Data will be presented by BOTOX treatment cycle according to the dose received at that treatment cycle (grouped to the nearest dose group, ie, 25 U, 50 U, or 100 U BOTOX), as well as by an overall BOTOX group (ie, regardless of dose).

For BOTOX treatment cycle 1, descriptive statistics will be provided by BOTOX dose for the daily average frequency of normalized daytime urinary incontinence episodes at study baseline and up to week 12 including change from study baseline. The treatment difference in mean change from study baseline for 100 U versus 25 U BOTOX and 50 U versus 25 U BOTOX will be calculated. Pairwise comparisons of 100 U versus 25 U BOTOX and 50 versus 25 U BOTOX at week 12, will be evaluated using an analysis of covariance (ANCOVA) model with study baseline value as covariate, and treatment group as a factor; 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).

For later BOTOX treatment cycles, week 12 after each treatment will be the timepoint of main interest and the efficacy variable of key focus is again change from study baseline in the daily average frequency of normalized daytime urinary incontinence episodes. For each BOTOX treatment cycle, descriptive statistics will be provided for the daily average frequency of normalized daytime urinary incontinence episodes at study baseline and each posttreatment visit. The change from study baseline and the 95% confidence intervals (CI) of the mean change will be provided.

Other efficacy analyses for the primary efficacy variable will include the proportion of patients achieving ≥ 50%, ≥ 75%, ≥ 90%, and 100% reduction from study baseline in daily average frequency of normalized daytime urinary incontinence at week 12 posttreatment 1. For BOTOX treatment cycle 1, the 100 U and 50 U BOTOX dose groups will be compared to the 25 U BOTOX group using the Cochran-Mantel-Haenszel (CMH) method controlling for baseline daytime urinary urgency incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day diary collection period).

Duration of effect will be evaluated as time from study drug administration to: a) patient's first request for subsequent treatment and b) qualification for subsequent treatment using a Kaplan-Meier survival analysis. Dose-response analyses will include a nonparametric area under the curve (AUC) analysis of daily average frequency of normalized daytime urinary incontinence episodes up to week 12 posttreatment 1.

Data from BOTOX treatment cycle 1 for the health outcomes parameter of PinQ will be analyzed using an ANCOVA model with study baseline value as covariate, and treatment group and stratification (baseline daytime urinary urgency incontinence episodes [a total of ≤ 6 episodes or > 6 episodes over the 2-day diary collection period]) as factors. For the modified TBS, the proportion of patients with a positive treatment response, defined as either "greatly improved" or "improved" will be presented and the 95% CI for the proportion of patients with a positive treatment response will be provided for each posttreatment visit. For later BOTOX treatment cycles, descriptive statistics for the PinQ score and modified TBS will be provided.

For safety variables, all safety analyses will be conducted on the BOTOX-treated population. Data will be presented by BOTOX treatment cycle according to the dose received at that treatment cycle, with all patients allocated to the nearest dose group (25 U, 50 U, or 100 U BOTOX), as well as by an overall BOTOX group (ie, regardless of dose).

Sample Size Calculation: The sample size calculation for this study is determined empirically. A total of approximately 108 patients are to be enrolled for the study (32 per treatment group plus 10% attrition).

The following table displays the estimated differences between 100 U BOTOX (maximum 6 U/kg) and 25 U BOTOX (maximum 6 U/kg) in mean daily average frequency of daytime episodes of urinary incontinence change from baseline at week 12 for a range of common standard deviations (SDs). All calculations assume 32 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 (Statistical Solutions Ltd., Cork, Ireland), and the CI for the difference of 2 means based on normal distribution.

Standard Deviation	Distance From Mean to the Limit
2.0	0.980
2.5	1.225
3.0	1.470
3.5	1.715
4.0	1.960

Note: The ranges of the SDs are determined based on the values from Allergan's 2 pivotal phase 3 OAB studies, 191622-095 and 191622-520. The estimate of the SD for the 100 U BOTOX treatment group is 3.33

for Study 191622-095, 3.58 for Study 191622-520, and 3.46 for the 2 studies combined. The distance from mean to limit indicates how much the CI for the mean extends from the observed difference in means in either direction.

Figure 1 **Visit Flow Chart**

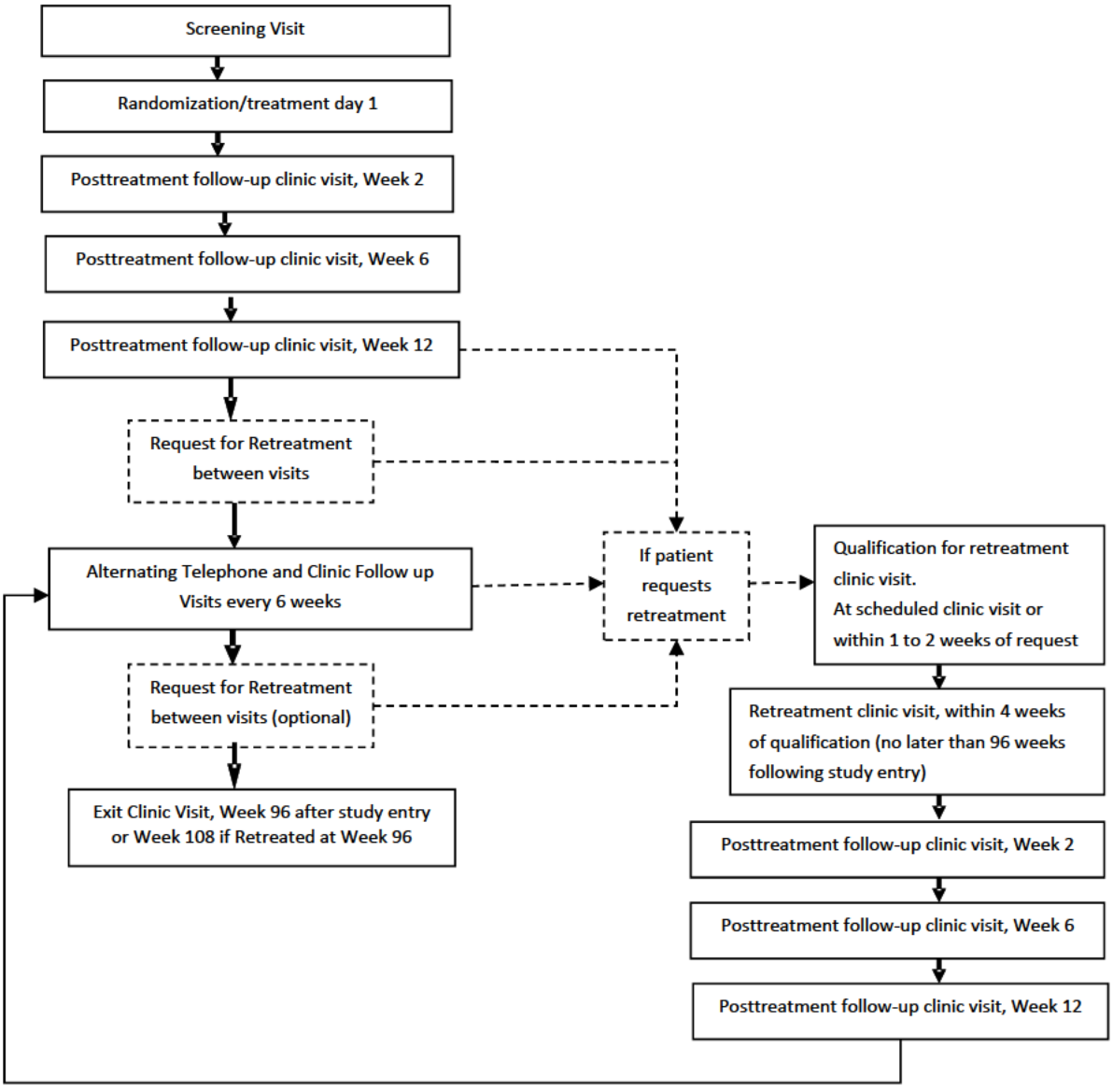


Table 1 Schedule of Visits and Procedures

	Screening[a]	Day 1 Randomization and treatment	Week 2 follow-up clinic visit	Week 6 follow-up clinic visit	Week 12 follow-up clinic visit	If no Request for Retreatment		
						Alternating telephone and clinic visits every 6 weeks (± 7 days)		Exit clinic visit
	(Day -28 to Day -1)[m]	(Within 28 days of start of screening procedures)[m]	(± 7 days)	(± 7 days)	(± 7 days)	Telephone visit	Clinic visit	96 weeks from day 1[i] (± 14 days)
Consent/authorization/assent	X							
Inclusion/exclusion criteria	X	X[c]						
Medical history	X							
Physical examination	X							X
Weight and height	X[b]	X[c]						X
Vital signs	X	X[c]	X	X	X		X	X
PVR urine	X[b]		X	X	X		X	X
Bladder and kidney ultrasound	X[b]							X
Urine dipstick	X	X[c]	X	X	X		X	X
Urinalysis/culture/sensitivity	X	X	X	X	X		X	X
Urine pregnancy test[f]	X	X[c]			X			X
Hematology and clinical chemistry		X[c]			X[d]			X
Immunogenicity sample		X[c]			X			X
Bladder diary	X		X	X	X		X	X
Reason for requesting retreatment[k]					X	X[l]	X	
Prophylactic antibiotics		X[c]						
Study treatment		X						
PinQ questionnaire		X[c]		X	X			
Modified TBS questionnaire				X	X			
Concomitant meds/procedures	X	X	X	X	X	X	X	X
Pretreatment adverse events	X	X[c]						
Posttreatment adverse events		X	X	X	X	X	X	X

	If Retreatment Requested/Received							
	Qualification for retreatment clinic visit[e]	Retreatment clinic visit[h]	Posttreatment follow-up clinic visits			Follow-up visits Alternating telephone and clinic visits every 6 weeks (± 7 days)		Exit clinic visit
	At scheduled clinic visits ≥ 12 weeks since prior treatment or between visits	Within 4 weeks since qualification and not > 96 weeks since day 1 (+ 7 days)	Week 2 (± 7 days)	Week 6 (± 7 days)	Week 12 (± 7 days)	Telephone visit	Clinic visit	96 to 108 weeks from day 1[j] (± 14 days)
Physical examination								X
Weight and height	X	X[c]						X
Vital signs	X[g]	X[c]	X	X	X		X	X
PVR urine	X[g]		X	X	X		X	X
Bladder and kidney ultrasound	X							X
Urine dipstick	X[g]	X[c]	X	X	X		X	X
Urinalysis/culture/sensitivity	X[g]	X	X	X	X		X	X
Urine pregnancy test[f]	X[g]	X[c]			X			X
Hematology and clinical chemistry		X[c]			X[d]			X
Immunogenicity sample		X[c]						X
Bladder diary	X[g]		X	X	X		X	X
Reason for requesting retreatment[k]	X				X	X[l]	X	
Prophylactic antibiotics		X[c]						
Study treatment		X						
PinQ questionnaire	X[g]			X	X			
Modified TBS questionnaire	X[g]			X	X			
Concomitant meds/procedures	X[g]	X	X	X	X	X	X	X
Adverse events	X[g]	X	X	X	X	X	X	X

PinQ = Pediatric Incontinence Questionnaire; PVR = post-void residual; TBS = Treatment Benefit Scale

[a] Screening period considered to have started at the time the first screening procedure is performed. Note: prohibited medication washout must be complete prior to the first screening procedure.

[b] May be performed during the screening period through day 1 (prior to randomization), excluding diary data collection days.

[c] Prior to treatment.

[d] Only includes complete blood count, serum blood urea nitrogen, and creatinine.

[e] Patient/parent/legally authorized representative can request retreatment from week 12 since their prior treatment, either at a scheduled clinic or telephone visit, or in between scheduled visits. If the request is made at a clinic visit and all qualification for retreatment criteria are fulfilled, then that visit will become the qualification for retreatment visit and the additional procedures will be performed, otherwise a qualification for retreatment clinic visit should be conducted within approximately 1 to 2 weeks of request and the qualification for retreatment criteria should be assessed prior to performing any other procedures. If the patient does not successfully qualify for retreatment they return to the visit schedule.

[f] Postmenarche females only.

[g] If the procedure/assessment has already been performed as part of a scheduled clinic visit, it is not repeated.

[h] If the patient is not treated at this visit eg, did not fulfill day of treatment criteria, a new retreatment visit should be scheduled as soon as possible, if applicable. Qualification for retreatment (or associated procedures) do not need to be repeated, but the day of treatment criteria will need to be fulfilled prior to treatment administration.

[i] For patients who do not request retreatment, exit occurs once 96 weeks from entry into the study at day 1 has occurred.

[j] Patients who request and receive retreatment will exit once 96 weeks from entry into the study has occurred, and at least 12 weeks follow-up since their last treatment has occurred; if a patient received retreatment at week 96, they would exit 108 weeks after day 1.

[k] If a request for retreatment is made, the patient/parent/legally authorized representative completes the “Reason for Requesting Retreatment” form indicating the main reason they are asking for another treatment.

[l] If a request for retreatment is made at a telephone visit, the patient will complete the form at the subsequent Qualification for Retreatment visit.

[m] An additional 7-day window is allowed for the screening period (ie, day -35 to day -1).

1. Background and Clinical Rationale

Overactive Bladder 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. Overactive bladder (OAB) is a syndrome that is characterized by bothersome lower urinary tract symptoms during the storage phase of bladder function. OAB is defined by the International Continence Society as "urgency, with or without urge incontinence, usually with frequency and nocturia" (Abrams et al, 2002). The most severe form of OAB results in urinary urgency incontinence. In children, the presence of one or all of the following symptoms: urgency, frequency, urge incontinence, and nocturia (which is less common in children than adults), is defined by the International Children's Continence Society as OAB (Nevéus et al, 2006).

OAB is the most common voiding dysfunction in children and appears to have a peak incidence between the ages of 5 and 7 years (Franco, 2008). In a study of 383 incontinent children ranging from 3 to 14 years of age with a female:male ratio of 60:40, the incidence of OAB was found to be 57.4% (Ruarte and Queseda, 1987). The prevailing theory in children is that OAB is believed to be a result of a delay in the acquisition of cortical inhibition over uninhibited detrusor contractions in the course of achieving a mature voiding pattern of adulthood (Franco, 2007). If OAB continues over a long period of time, thickening of the bladder wall can result, which will have an impact in adulthood. As patients become older, the consequences become more profound and require more effort to correct (Fitzgerald et al, 2006; Minassian et al, 2006).

Currently Available Treatments for Overactive Bladder in Children

Initial treatment of OAB in children consists of lower urinary tract rehabilitation, mostly referred to as urotherapy. This includes providing information about and demystifying lower urinary tract function, and advice regarding normal voiding habits, fluid intake, and preventing constipation. In addition, children with OAB may be offered physiotherapy (eg, pelvic floor exercises), receive training in biofeedback, or alarm therapy (Tekgül et al, 2012). The addition of anticholinergics may provide some additional relief; however, the results of some recently published randomized controlled clinical trials of anticholinergics in children with OAB have yielded conflicting results. One trial on tolterodine showed safety but not efficacy (Nijman et al, 2005), while another trial on propiverine showed both safety and efficacy (Marschall-Kehrel et al, 2009). Although the use of anticholinergics is

recommended (Tekgül et al, 2012), it is well known that the use of anticholinergics for this condition can also be associated with problematic side effects. Furthermore, in children who experience wetting on a daily basis, the likelihood that anticholinergics would be effective was found to be only 20% (Van Arendonk et al, 2006). Other therapies are invasive, including surgically implanted neuromodulation devices or surgical augmentation of the bladder. 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 Overactive Bladder

BOTOX (Botulinum Toxin Type A purified neurotoxin complex [United States (US) adopted name onabotulinumtoxinA]) inhibits synaptic vesicle-mediated neurotransmission through the cleavage of SNAP-25 (synaptosomal protein of molecular weight 25 kilodaltons [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 Patients with Overactive Bladder

Allergan has completed a clinical development program for the use of BOTOX in adult patients with urinary incontinence due to OAB, and it is licensed for use in many countries. Where registered, the licensed dose in adults is 100 units (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 (Study 191622-077) that evaluated a range of BOTOX doses (50 U, 100 U, 150 U, 200 U, and 300 U) versus placebo (N = 313). This study demonstrated improvements in OAB symptoms and urodynamic parameters at doses of 100 U and above. This was also reflected in consistent improvements in patient-reported health-related quality of life (HRQOL) at doses of 100 U and above. A dose-dependent safety profile was identified with respect to adverse events of urinary retention and urinary tract infection (UTI), as well as in post-void residual (PVR) urine volume and use of clean intermittent catheterization (CIC). The benefit/risk profile evaluation across the doses resulted in the selection of 100 U as the appropriate dose for the pivotal phase 3 studies. Based on these phase 2 results, a phase 3 program was subsequently initiated that included 2 identical pivotal phase 3 studies in OAB patients who were not adequately managed with anticholinergic therapy (Study 191622-095, N = 557 and Study 191622-520, N = 548). Patients in both studies received 100 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 100 U BOTOX for this retreatment. Patients were to remain in the studies for at least 24 weeks, and those receiving a second treatment were to be followed for at least 12 weeks posttreatment 2. In addition, patients could enter a long-term extension study (Study 191622-096, 3 years duration) in which they could receive multiple treatments of BOTOX (100 U or, if certain additional criteria were met, 150 U BOTOX). Currently, Study 191622-096 is still ongoing; however, data from interim analyses are available.

Both pivotal phase 3 studies achieved both co-primary efficacy endpoints of significant reductions in urinary incontinence at week 12 and a significantly higher proportion of patients reporting their condition as improved or greatly improved on the Treatment Benefit Scale (TBS). Reductions in urinary incontinence of approximately 2.5 to 3.0 episodes per day were observed in the 100 U BOTOX treatment groups compared with approximately 1 episode per day in the placebo groups. The proportion of patients with a positive treatment response on the TBS in each pivotal phase 3 study at week 12 was approximately 60% in the

100 U BOTOX dose group, whereas in the placebo group it was approximately 28% (Nitti et al, 2013; Chapple et al, 2013). In addition, all secondary endpoints were met in both pivotal studies, which included OAB symptoms and other HRQOL parameters. The duration of effect of BOTOX, based on the first 100 U BOTOX treatment cycle of the pooled phase 3 data integrated with the long-term extension study data, was approximately 6 months.

With respect to safety, adverse events were primarily local adverse events related to the urinary tract, in particular urinary retention and UTI. Treatment with 100 U BOTOX was associated with a transient increase in PVR urine volume, although the majority of patients did not have an increase greater than 100 mL. The limited effect of 100 U BOTOX on PVR was reflected in only 6.5% of patients initiating CIC posttreatment (compared to 0.4% in the placebo group) and the low urinary retention rates.

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, UTI 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 150 U BOTOX dose compared with the 100 U BOTOX dose, and given that the 100 U BOTOX dose displayed a better safety profile, 100 U BOTOX was submitted for licensing registration, and approval has subsequently been granted in many countries at this dose.

Use of BOTOX in Pediatric Patients with Overactive Bladder

Following the development of BOTOX for use in adults with urinary incontinence due to OAB, the purpose of Study 191622-137 is to assess the safety and efficacy of BOTOX for the treatment of urinary incontinence in the OAB pediatric population. In this study, patients will receive 25 U, 50 U, or 100 U BOTOX and will have the opportunity to receive multiple treatments over approximately 2 years, with the possibility of dose adjustment based on patient response. The pediatric population to be studied, following discussion with the US Food and Drug Administration (FDA), was defined as patients aged 12 to 17 years.

The doses selected in this pediatric study provide a sufficient range to assess dose-response while not exceeding the adult dose of 100 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 (further information on these studies can be found in the BOTOX Investigator's Brochure). There are data from published literature in which doses above those proposed in

this study have been used in the pediatric population, mostly in patients with neurogenic OAB (eg, 300 U and 10 U/kg [Gamé et al, 2009; Sager et al, 2012]). Currently, only 2 small studies have been conducted with BOTOX in pediatric patients with OAB not adequately managed with anticholinergics. The first study, reported by Hoebeke et al (2006), evaluated 100 U BOTOX in 21 children aged between 8 and 14 years (mean, 10.8 years). The other study was conducted by Marte et al (2010) in 21 children aged between 8 and 12 years (mean, 10.2 years) with a dose of 200 U BOTOX. To date, no dose-ranging studies have been conducted in the pediatric OAB population.

In addition to evaluating the optimal dose of BOTOX in this patient population, this study is designed to collect long-term safety and efficacy data from repeated treatments over a period of approximately 2 years. Of note, Allergan is currently conducting a study (Study 191622-120 and its extension, Study 191622-121) of BOTOX in pediatric patients with urinary incontinence due to neurogenic detrusor overactivity that will evaluate doses of 50 U, 100 U, and 200 U BOTOX; the studies are ongoing.

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

To evaluate the safety and efficacy of BOTOX for the treatment of urinary incontinence due to OAB in patients 12 to 17 years of age who have not been adequately managed with anticholinergic therapy. To evaluate the safety and efficacy of repeated BOTOX treatments in this patient population.

2.2 Clinical Hypotheses

BOTOX (1 or more of the treatment groups) has an acceptable safety profile when injected into the detrusor of patients 12 to 17 years of age with OAB. BOTOX (1 or more of the treatment groups) improves the symptoms of OAB as measured by a reduction from baseline in daytime urinary incontinence episodes.

3. Study Design

This is a multicenter, randomized, double-blind, parallel-group, multiple-dose study to evaluate the efficacy and safety of BOTOX in patients with urinary incontinence due to OAB who are 12 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 once all "day of treatment criteria" are fulfilled (see Section 5.9.1). Patients will initially be randomized via a central interactive voice response system (IVRS)/interactive web response system

(IWRS) and assigned a randomization number prior to treatment in a 1:1:1 ratio to receive a single treatment of 25 U, 50 U, or 100 U BOTOX (not to exceed 6 U/kg). Randomization will be stratified by baseline daytime urinary urgency incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day bladder diary collection period). During the screening period and on the days of bladder diary completion prior to scheduled clinic visits during the study, patients agree to a minimum fluid intake of 1500 mL/m^2 body surface area (BSA) and a maximum of 3000 mL/m^2 BSA per day. 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 who do not request retreatment will have alternating telephone and clinic follow-up visits every 6 weeks until they exit the study. In this study, patients can receive multiple treatments dependent upon the number and timing of patient requests/qualification for retreatment. Before receiving each retreatment patients will have to meet the qualification and "day of treatment criteria". The dose received at any given retreatment will be determined by the investigator based on the response to the preceding blinded treatment. The investigator can elect to keep the dose the same or increase the dose compared with the preceding treatment (if it is deemed a decrease in dose is warranted, the patient will be exited from the study). The actual dose received remains blinded (unless the patient is requested to exit the study via the IVRS/IWRS, as described at the end of Section 5.5, or until the primary analysis has been reported as described in Section 7.7).

Request for retreatment can occur at any scheduled clinic or telephone visit or between scheduled visits from week 12 onwards. If a request occurs at a scheduled clinic visit, then that clinic visit will also become the qualification for retreatment visit, otherwise a qualification for retreatment clinic visit should occur within approximately 1 to 2 weeks of request. Patients exit the study once 96 weeks have elapsed since entry on day 1 and at least 12 weeks follow-up since their last study treatment has occurred (exit will therefore be between 96 and 108 weeks since study entry on day 1; the latter being for patients who received retreatment at week 96).

The primary efficacy measure is daytime urinary incontinence episodes, and the primary timepoint is week 12 after treatment 1.

4. Study Population and Entry Criteria

4.1 Number of Subjects

Approximately 108 patients will be randomized at approximately 35 to 45 sites in order to have an estimated 96 patients (32 per treatment group) based on an anticipated dropout rate of 10% by the primary timepoint of week 12 after treatment 1.

4.2 Study Population Characteristics

This study will include patients 12 to 17 years of age with urinary urgency incontinence due to OAB who have not been adequately managed with anticholinergics.

4.3 Inclusion Criteria

The following are requirements for entry into the study:

1. written informed consent has been obtained from the legally authorized representative and written minor assent has been obtained, in accordance with local laws and institutional review board (IRB)/independent ethics committee (IEC) requirements
2. written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information (US sites) and written Data Protection consent (European sites)
3. male or female, aged ≥ 12 years to ≤ 17 years of age at the time of informed consent
4. patient has symptoms of OAB (frequency and urgency) with urinary incontinence for a period of at least 6 months immediately prior to screening, determined by patient history
5. patient experiences a total of ≥ 2 episodes of daytime urinary urgency incontinence in the 2-day patient bladder diary completed during the screening period (daytime is defined as time between waking up to start the day and going to bed to sleep for the night)
6. patient experiences urinary frequency, defined as an average of ≥ 8 micturitions (toilet voids) per day ie, a total of ≥ 16 micturitions in the 2-day patient bladder diary completed during the screening period

7. patient has not been adequately managed with 1 or more anticholinergic agents for the treatment of OAB in the opinion of the investigator. This includes patients who are still incontinent despite anticholinergic therapy, experiencing intolerable side effects, or are unwilling to continue to take the medication for any reason.
8. patient is willing and able to use CIC to empty the bladder at any time after study treatment if it is determined to be necessary by the investigator
9. patient agrees to a minimum fluid intake of 1500 mL/m^2 BSA, not to exceed 3000 mL/m^2 BSA per day, during the patient bladder diary completion days at screening and prior to clinic visits during the study (see Section 6.3.6 for further details)
10. negative urine pregnancy test for females who are postmenarche
11. patient is able to complete study requirements including completion of bladder diaries and HRQOL questionnaires (these can also be completed by the parent/legally authorized representative), and is likely to attend study visits in the opinion of the investigator

4.4 Exclusion Criteria

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

1. patient has an uncontrolled systemic disease, or has previous or current diagnosis of malignancy
2. patient has symptoms of OAB due to any known neurological reason (eg, spina bifida, spinal cord injury, or cerebral palsy)
3. patient has a history of 2 or more UTIs treated with antibiotics within 6 months of randomization/day 1 or is taking prophylactic antibiotics to prevent chronic UTI
4. patient has a history or evidence of any pelvic or urological abnormalities, except OAB, including:
    - bladder neck surgery resulting in an open bladder neck, or reconstructive surgery of the lower urinary tract (eg, urostomy, urinary diversion, or bladder augmentation)
    - anatomical evidence of bladder outlet obstruction (including functional outlet obstruction), urethral or urethral valve obstruction/stricture at screening

- surgery of the urinary tract (including minimally invasive surgery) within 6 months of screening (except those listed above which are exclusionary for any time period)
- circumcision within 1 month of screening
- clinically relevant kidney abnormality, or clinically relevant vesicoureteric reflux, or disease of the bladder (other than OAB) that may affect bladder function

5. patient has predominance of stress incontinence, or "giggle" incontinence, or any condition other than OAB that in the investigator's opinion may account for the patient being incontinent
6. patient has unmanaged, unresolved bowel problems (eg, constipation, encopresis)
7. patient currently uses or plans to use medications or therapies to treat symptoms of OAB, including nocturnal enuresis or nocturia. Patients previously receiving these medications must have discontinued their use prior to the start of the first screening procedure as follows:
    - for desmopressin, at least one day prior
    - for anticholinergic therapy, at least 7 days prior
    - for intravesical anticholinergic therapy, at least 4 weeks prior
    - for mirabegron, at least 14 days prior
8. patient currently uses or plans to use an implantable or nonimplantable electrostimulation/neuromodulation device for treatment of OAB. (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.)
9. patient plans to start using psychiatric medications or medications for attention deficit hyperactivity disorder during the study. If the patient is already using such medications they should be on a stable dose prior to randomization/day 1 and agree to remain on the same dose during the study if possible when medically indicated.
10. patient uses CIC or an indwelling catheter to manage their OAB
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

12. patient has been treated with intravesical capsaicin or resiniferatoxin within 12 months of screening
13. patient has a PVR urine volume of > 40 mL at screening. The PVR measurement can be repeated once on the same day; the patient is to be excluded if the repeated measure is above 40 mL.
14. patient has a daytime (waking hours) total volume of urine voided > 3000 mL, collected over one daytime period during the 2-day bladder diary collection period prior to randomization/day 1
15. postmenarche female patients of childbearing potential who are pregnant, nursing, or planning to become pregnant during the study (postmenarche female patients must also either be sexually abstinent or use another acceptable form of contraception – see Section 4.5.1.1)
16. patient has known allergy or sensitivity to components of any botulinum toxin preparation (including the study medication preparation), anesthetics or antibiotics to be used during the study
17. patient has hemophilia, or other clotting factor deficiencies, or disorders that cause bleeding diathesis
18. patient cannot withhold any antiplatelet, anticoagulant therapy, or other medications with anticoagulant effects for 3 days prior to randomization/day 1. Note: some medications may need to be withheld for > 3 days, per clinical judgment of the investigator (see Section 4.5.2, Prohibited Medications/Treatments for additional details)
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
20. current enrollment in an investigational drug or device study, or participation in such a study within 30 days of entry into this study (or longer if local requirements specify)
21. patient has a condition or is in a situation which in the investigator's opinion may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study

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.

If the patient is already using psychiatric medications or medications for attention deficit hyperactivity disorder, they should have been on a stable dose prior to randomization/day 1 and agree to remain on the same dose during the study if possible when medically indicated.

Use of antihistamines and/or decongestants (sympathomimetics) is permitted to treat upper respiratory infections or allergies after study treatment has been administered.

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

If the permissibility of a specific medication/treatment is in question, please contact Allergan.

4.5.1.1 Definition of Females of Childbearing Potential and/or 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.

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.

Anticholinergics or any other medications (including sympathomimetic medications) used for the treatment of symptoms of OAB, including nocturnal enuresis or nocturia, are prohibited throughout study participation. Desmopressin use is prohibited within 1 day of the start of the screening period procedures. Anticholinergic therapy is prohibited within 7 days of the start of the screening period procedures, or within 4 weeks if administered intravesically. Mirabegron is prohibited within 14 days of the start of the screening period procedures.

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 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 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, netilmicin sulfate, and 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.

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

5. Study Treatments

5.1 Study Treatments and Formulations

BOTOX

Each vial of BOTOX (Botulinum Toxin Type A) purified neurotoxin complex, formulation No. 9060X (US Adopted Name is OnabotulinumtoxinA), contains: 100 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 dose (LD_{50}) in mice of the reconstituted BOTOX injected intraperitoneally. The study medication will be reconstituted with 0.9% sodium chloride (preservative-free).

5.2 Control Treatment

There is no control treatment in this study.

5.3 Methods for Blinding

Both patients and investigators will remain blinded to BOTOX dosage (unless the patient is requested to exit the study via the IVRS/IWRS due to dosing request, as described at the end of Section 5.5).

The study medication will be packaged and labeled in identically appearing vials and reconstituted to the same volume 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 the number of daytime urinary urgency 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 25 U, 50 U, or 100 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 IVRS/IWRS. Study medication will be labeled with medication kit numbers and the IVRS/IWRS will provide the IDR with a specific medication kit number and treatment group assignment for the patient.

Patients who request and qualify for retreatment will receive a blinded dose of 25 U BOTOX (not to exceed 6 U/kg), 50 U BOTOX (not to exceed 6 U/kg), or 100 U BOTOX (not to exceed 6 U/kg). The dose received will be dependent on the assessment of the clinical response (efficacy and safety) to the previous blinded study treatment. The patient/parent/ legally authorized representative will be questioned on the patient's treatment response to establish if, in their opinion, the current treatment response is adequate or if there was little or no treatment benefit and whether they would be willing/want to move to a higher dose. They will also be questioned on whether the patient is experiencing side effects. Using this information, the investigator will use his/her own clinical assessment of the patient and apply the following criteria for the retreatment dose request:

- if the benefit/risk balance is evaluated by the investigator to be appropriate at the current dose, then the same dose would be requested
- if the investigator assessed that, although the preceding dose was well tolerated, the response received was insufficient and warrants a higher dose, then a dose increase would be requested
- if the investigator assessed that there were side effects that would warrant a lower dose, the patient would be exited from the study

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

- elect to keep the same dose as received at the previous treatment (not to exceed 6 U/kg)
- elect to increase the dose compared to the previous treatment (not to exceed 6 U/kg):
  - if the patient received 25 U BOTOX at the previous treatment, they would receive 50 U BOTOX
  - if the patient received 50 U BOTOX at the previous treatment, they would receive 100 U BOTOX
  - if the patient received 100 U BOTOX at the previous treatment, they would remain at 100 U BOTOX (after 2 requests, when the patient has already received 2 treatments of 100 U BOTOX, they would be exited; see below)

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

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

- for any patient who is already on the highest dose (100 U), if a dose escalation is requested by the investigator on 2 occasions, the patient will be exited from the study upon the second escalation request without receiving any further treatments
- for any patient on any dose, if the investigator assesses that they should not be retreated with the current dose but that a dose reduction would be warranted, the patient will be exited from the study as a reduction of dose in this study is not an option

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

Note that retreatments will be blinded until completion of the primary analysis, after which time the investigators will be unblinded to the patients' initial treatment assignments (see Section 7).

5.6 Treatment Regimen and Dosing

Patients can receive multiple retreatments in this study.

All eligible patients enrolled into the study will receive a double-blind treatment of either 25 U BOTOX (not to exceed 6 U/kg), 50 U BOTOX (not to exceed 6 U/kg), or 100 U BOTOX (not to exceed 6 U/kg) for treatment 1.

All patients eligible for retreatment will receive either 25 U BOTOX (not to exceed 6 U/kg), 50 U BOTOX (not to exceed 6 U/kg), or 100 U BOTOX (not to exceed 6 U/kg). The dosage used at each retreatment will be determined as described in Section 5.5.

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

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

5.7 Storage of Study Medications

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

The vacuum-dried study medication must be stored in a refrigerator at a temperature between 2 and 8°C. Refer to the Pharmacy Manual for guidelines on acceptable variances and instructions for reporting to Allergan. If not used immediately (ie, within 30 minutes of reconstitution) reconstituted study medication, either in the vial or the dosing syringe, must also be stored in a refrigerator at a temperature between 2 and 8ºC, and is to be used within 4 hours following reconstitution. Storage conditions will be documented. If not used within 4 hours of reconstitution, study medication should be disposed of as described in the Pharmacy Manual.

5.8 Preparation of Study Medications

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

Administration of the first study treatment should occur within 28 days of the start of the screening procedures. For patients who request retreatment, study treatment will be administered within 4 weeks of qualification for retreatment (see Section 5.10.1 for qualification for retreatment criteria), but no later than 96 weeks since study enrollment on day 1 of this study. The following "day of treatment criteria" must be fulfilled prior to the administration of study medication:

- central laboratory urine analysis results and, if applicable, urine culture and sensitivity results for possible UTI have been reviewed
- negative urine dipstick reagent strip test (for nitrites and leukocyte esterase) on the day of treatment
- patient is asymptomatic for a UTI on the day of treatment, in the opinion of the investigator
- 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)
- for patients who request retreatment, PVR urine volume confirmed to be < 200 mL at the qualification for treatment visit
- 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

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

5.9.2 Prophylactic Antibiotics

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

Note: Independent from the above description for prophylactic antibiotics, if a UTI is identified from the urinalysis/culture obtained during the screening period, the UTI must be treated with an antibiotic to which the identified bacteria is sensitive per local site practice. As per the day of treatment criteria described in Section 5.9.1, the patient must not have a UTI on the day of treatment, in the opinion of the investigator.

5.9.3 Use of Anesthesia

Anesthesia will be used for all patients during the treatment administration. The choice of general or local anesthesia is at the discretion of the investigator and the preference of the patient/legally authorized representative.

If general anesthesia is to be used it will be administered per local site practice (including prior sedation if deemed medically necessary) by an appropriately qualified anesthesiologist; however the use of neuromuscular blocking agents is not permitted.

Patients who undergo the treatment procedure under local anesthesia may do so with or without sedation at the discretion of the investigator and per local site practice. Local anesthesia of the bladder will be achieved by instillation of 1% to 2% lidocaine (or similar acting local anesthetic) into the bladder 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.

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

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 during the screening period from the bladder scan/ultrasound or on the day of treatment upon cystoscopy 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 and until a spontaneous void has occurred (or longer, depending upon 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/legally authorized representatives will be instructed to contact the study site if the patients 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.

5.10 Retreatment

Patients can receive multiple retreatments in this study (between 1 and 7 at 25 U, 50 U, or 100 U BOTOX; not exceeding 6 U/kg). For each retreatment, patients must fulfill the qualification for retreatment criteria described in Section 5.10.1. In addition, prior to treatment administration the day of treatment criteria must be fulfilled, as described in Section 5.9.1.

5.10.1 Qualification for Retreatment Criteria

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

Patients/parents/legally authorized representatives can request retreatment at any scheduled clinic or telephone visit from week 12 onwards , 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/legally authorized representative requests retreatment
- patient has at least 1 daytime urinary urgency incontinence episode over the 2-day bladder diary collection period
- PVR urine volume must be < 200 mL
- at least 12 weeks have elapsed since previous treatment
- patient has not experienced a treatment-related serious adverse event at any time

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

6. Response Measures and Summary of Data Collection Methods

6.1 Efficacy Measures

6.1.1 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 12 after treatment 1. For patients who receive multiple treatments in this study, the timepoint of main focus is week 12 after each treatment.

6.1.2 Secondary Efficacy Measures

The following secondary efficacy measures will be collected after each treatment using the bladder diary:

- number of daytime micturition episodes
- number of daytime urgency episodes
- presence or absence of night time urinary incontinence
- volume voided per micturition

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

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

6.1.3 Health Outcomes Measures

Two questionnaires will be utilized in this study:

- Pediatric Incontinence Questionnaire (PinQ) score
- modified Treatment Benefit Scale (TBS)
    - the proportions of patients whose condition is rated as either "greatly improved" or "improved" will be determined

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

6.2 Safety Measures

- adverse events
- serious adverse events
- physical examination findings
- vital signs (pulse rate, blood pressure, respiration rate, and body temperature)
- urine dipstick reagent strip test
- urinalysis (with urine culture/sensitivity, as applicable)
- hematology and clinical chemistry
- immunogenicity testing
- kidney and bladder ultrasound
- PVR volume
- urine pregnancy test for females who are postmenarche
- concomitant medications
- concurrent procedures

6.3 Examination Procedures, Tests, Equipment, and Techniques

Screening procedures can commence once the parental/legally authorized representative 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 1 visit.

6.3.1 Medical History

The patient's medical history (including diagnosis or symptom, date of onset, current status) and associated surgical procedures (including name of procedure and date of surgery) will be documented at screening.

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

6.3.2 Physical Examination

The investigator 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, and throat), heart/cardiovascular, lungs, abdomen, neurologic, extremities, back, musculoskeletal, lymphatic, skin, genitourinary, and other findings.

6.3.3 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, at the qualification for retreatment clinic visits if the patient qualifies, on each day of treatment prior to the injection procedure, and at the exit visit.

6.3.4 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.

6.3.5 Bladder Diary

Patients/parents/legally authorized representatives will collect bladder diary data over 2 consecutive days during screening and in the week prior to each posttreatment study clinic visit (with a +3 day window, if required) when the patient is not at school (or equivalent) for the full day (eg, at the weekend). For screening, the bladder diary can be completed for 2 consecutive days (nonschool, or equivalent) at any time during the screening period. The same person(s) (patient/parent(s)/legally authorized representative) 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 legally authorized representative 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) of each voiding episode during the daytime (time between waking up to start the day and going to bed to sleep for the night) and each daytime urgency episode
- volume of each void measured over one daytime (waking hours) period during the 2-day bladder diary collection period. This will be used to calculate the total volume voided and the average volume voided per micturition (see Sections 6.3.7 and 6.3.8)
- 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/legally authorized representative.

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

6.3.6 Minimum/Maximum Fluid Intake

During the patient bladder diary completion days at screening and prior to clinic visits during the study the patient agrees to a minimum fluid intake of 1500 mL/m^2 BSA, not to exceed 3000 mL/m^2 BSA per day. Investigators will be provided with worksheets to perform the fluid intake per BSA calculation (see the Study 191622-137 Study Manual). The Mosteller formula will be used in the calculation of BSA using the patient's height and weight at screening as follows:

BSA (m^2) = √([height (cm) × weight (kg)]/3600) (Mosteller, 1987).

6.3.7 Total Volume Voided

The total volume of voided urine will be measured by all patients over one daytime (waking hours) period during the 2-day bladder diary collection period. Urine collection containers needed to perform this measurement will be supplied to the patients. Patients are to measure the volume of each void as it occurs and enter that amount (with time of void) into their diary. Instructions on the total volume voided collection procedure can be found in Attachment 12.3 and the Study Manual.

6.3.8 Volume Voided Per Micturition

Average volume voided per micturition will be determined from the total volume voided measured over one daytime (waking hours) period during the 2-day bladder diary period, divided by the number of individual entries of volume voided in the same daytime period.

6.3.9 Post-void Residual (PVR) Urine Volume

PVR urine volume is assessed at screening and at every posttreatment clinic visit by ultrasound or bladder scan after the patient has performed a voluntary void. PVR urine volume can be assessed at any other time depending on clinical need. PVR measurements will not be done by catheterization.

Should a PVR urine volume indicate a clinically meaningful elevation (as defined below), the patient should be asked to void once again (allowing the patient sufficient time to void). The

PVR urine volume will then be re-assessed. For patients who have a PVR urine volume measurement repeated, only the repeat value should be recorded in the eCRF.

Guidance on how to manage an elevated PVR, observed at any routine study visit or unscheduled visit is provided. In summary, posttreatment PVR urine volume is divided into 3 categories:

i) < 200 mL

ii) between ≥ 200 mL and < 350 mL

iii) ≥ 350 mL

Protocol required action depends on the PVR category as does the need for further visits to evaluate the patient. Protocol-required need for CIC is also dependent on the PVR as well as the patient symptoms. This guidance is to ensure patients are appropriately followed up and CIC is only initiated when required (while also ensuring any unnecessary intervention is limited). Further details are given below.

This guidance does not preclude further actions if the investigator deems it necessary.

i) PVR < 200 mL

No protocol required action needs to be taken. Patient continues to be reviewed as per the schedule of visits and procedures.

ii) PVR ≥ 200 mL and < 350 mL

If a PVR of ≥ 200 mL but < 350 mL is identified at any posttreatment visit, the investigator will assess the patient for any spontaneously reported associated symptoms (such as voiding difficulties or sensation of bladder fullness), with the resulting action to be as follows:

a) If a patient reports associated symptoms that in the opinion of the investigator requires CIC to be initiated, then CIC should be managed as detailed in the CIC section.

b) If a patient does not report any symptoms or if they report associated symptoms that, in the opinion of the investigator, do not require CIC then the following will occur:

- The patient will be seen for an additional follow-up visit 1 week later, at which time the PVR and any associated symptoms will be reassessed and a urine dipstick, central laboratory urine analysis, and culture/sensitivity will be performed. At this reassessment visit:

    - If the PVR is increasing and is associated with symptoms, that in the investigator's opinion require CIC, then CIC should be initiated and managed as detailed below in the CIC section

    - If the PVR is ≥ 350 mL then CIC should be initiated and managed as detailed below in the CIC section

    - If the PVR is increasing but is not associated with symptoms or is associated with symptoms that in the opinion of the investigator do not require CIC, then the patient will be seen 1 week later to determine if CIC has become warranted and should be initiated based on PVR and/or any associated symptoms. At this additional reassessment visit:

        - A urine dipstick, central laboratory urine analysis and culture/sensitivity will be collected

        - If in the investigator's judgment CIC should be initiated, then CIC should be managed as detailed below in the CIC section

        - If CIC is not initiated and PVR continues to increase, the investigator will determine whether the patient will be followed at regularly scheduled study visits or whether additional follow-up visits should occur

    - If the PVR is decreasing or is unchanged then the patient will continue to be reviewed as per the schedule of visits and procedures.

iii) PVR ≥ 350 mL

If a PVR of ≥ 350 mL is identified at any posttreatment visit (regardless of symptoms) then CIC will be initiated as detailed in the CIC section.

Clean Intermittent Catheterization

The following guidance should be used for the initiation and cessation of CIC in this study. Sterile, single-use intermittent catheters should be used. Indwelling catheters should not be used in this study, therefore the Allergan Medical Safety Physician should be informed if an indwelling catheter is utilized.

Initiation of Clean Intermittent Catheterization

As described above in the PVR section, CIC should be initiated when one of the following criteria is fulfilled:

- PVR is ≥ 350 mL at any posttreatment visit, regardless of whether the patient reports associated symptoms
- PVR is ≥ 200 mL and < 350 mL and the patient spontaneously reports associated symptoms (ie, voiding difficulties, sensation of bladder fullness) that in the opinion of the investigator requires CIC

The following will occur when initiating CIC:

1. CIC is implemented and the patient should be instructed to perform CIC using sterile, single-use catheters (which will be provided to the patient)
2. An adverse event of urinary retention is recorded
3. Urine dipstick, central laboratory urine analysis and culture/sensitivity are performed as per routine requirements at each study visit
4. The patient will be seen for a follow-up visit 1 week later where the PVR, associated symptoms, urine dipstick, central laboratory urine analysis and culture/sensitivity will be reassessed. The investigator will determine whether the patient can then be followed at regularly scheduled study visits or whether additional follow-up visits should occur.

Cessation of Clean Intermittent Catheterization

CIC should only be discontinued when the following criteria are fulfilled:

- The patient does not have any associated symptoms which in the opinion of the investigator require CIC AND

- The PVR is < 350 mL.

Upon discontinuing CIC the patient will be seen for a follow-up visit 1 week later where the PVR, associated symptoms, urine dipstick, central laboratory urine analysis and culture/ sensitivity will be reassessed. The investigator will determine whether the patient can then be followed at regularly scheduled study visits or whether additional follow-up visits should occur based on PVR and/or associated symptoms.

These criteria should ensure that CIC is initiated and discontinued when appropriate to do so.

6.3.10 Adverse Events of Urinary Retention and Residual Urine Volume

Protocol-specific definitions for adverse events of urinary retention and residual urine volume are provided in Section 9.1.2 (Study-specific Definitions for Particular Adverse Events).

The investigator should use the information from the regular assessment of PVR urine volume and the need to catheterize for urinary retention/elevated PVR to assess the stop date of these adverse events.

6.3.11 Bladder and Kidney Ultrasound

Ultrasound of the bladder and kidneys will be performed during the screening period (which for this evaluation can include prior to randomization on day 1), at the qualification for retreatment clinic visit, and 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).

6.3.12 Dipstick Reagent Strip Test (Urine Dipstick)

The urine dipstick is used to identify a potential UTI (see below for definition of UTI adverse event) and to provide immediate information to the investigator. The investigator may initiate empirical treatment with antibiotics if deemed necessary, however, the required urine samples must also be sent to the central laboratory.

Urine dipstick tests are performed in conjunction with a central laboratory urine analysis and urine culture/sensitivity test. In some cases, with Allergan approval, a local laboratory may be used for urine testing parameters.

Screening Urine Dipstick Reagent Strip Test Results:

If a patient has a positive dipstick test for nitrites or leukocyte esterase, and the bacterial infection is confirmed by the central laboratory urine analysis and urine culture and sensitivity test (bacteriuria count of > 10^5 colony forming units [CFU]/mL conjoint with a leukocyturia of > 5/high powered field [hpf]), the patient should be treated with antibiotics as determined by the investigator.

Day of Treatment Urine Dipstick Reagent Strip Test Results:

Patients with a positive dipstick test for nitrites or leukocyte esterase indicating a potential infection at randomization/day 1 or at any subsequent treatment visits must not receive any study treatment until results of the central laboratory urine analysis and urine culture/sensitivity test are obtained. If a bacterial infection is confirmed, the patient should be treated with antibiotics as determined by the investigator. The patient may return for a rescheduled randomization/day 1 visit (within 28 days of screening) or a retreatment visit (if the patient has requested and qualified for retreatment) and receive study treatment once a dipstick confirms a negative result for infection and all the "day of treatment criteria" are fulfilled.

Posttreatment and Exit Visit Urine Dipstick Reagent Strip Test Results:

Positive urine dipstick reagent strip test results at posttreatment visits will be confirmed by the central laboratory urine analysis and urine culture/sensitivity test which is also performed at every study visit. The patient will be treated with antibiotics as determined by the investigator.

6.3.13 Urinalysis, Culture, and Sensitivity

A urine sample for urinalysis by a central laboratory will be taken during the screening period and at all clinic visits. A urine culture and sensitivity test will be performed when central laboratory urine results are suggestive of a UTI (positive leukocyte esterase, nitrites, blood and/or microscopic sediments such as white blood cells [WBCs], red blood cells [RBCs] and/or bacteria). An additional urine sample may be taken by the site at the same time for local analysis.

Only the central laboratory data will be used for the statistical analysis.

Note: If a UTI (as defined in Section 9.1.2) is identified from the urinalysis/culture obtained during the screening period or at the qualification for retreatment visit, the UTI must be treated with an antibiotic to which the identified bacteria is sensitive per local site practice.

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

6.3.13.1 Adverse Events of Urinary Tract Infection

Please refer to Section 9.1.2 for the study-specific definition of UTI adverse events. If a patient meets the criteria for the definition of a UTI, the investigator will record whether the UTI was "symptomatic" or "asymptomatic" on the adverse event eCRF.

If a patient reports a UTI to the investigator that was evaluated by a physician not at the investigative site (eg, primary care physician or emergency room), then all reasonable attempts will be made to obtain the confirmatory urine analysis and culture/sensitivity results. In such instances, the UTI should still be captured on the adverse event eCRF.

6.3.14 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 prior to each treatment administration (if no general anesthesia is to be administered a blood sample is taken prior to treatment). A blood sample will also be taken at week 12 after each treatment and at study exit.

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.

6.3.14.1 Renal Function Testing

Renal function will be monitored from an estimate of the glomerular filtration rate (eGFR) determined from the serum creatinine levels obtained on the day of each treatment (prior to treatment), week 12 after each treatment, and at study exit.

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

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

6.3.15 Immunogenicity Testing

Blood samples for immunogenicity testing will be collected prior to each treatment administration, at week 12 after treatment 1, and at study exit.

Serum samples will be collected and stored at -20 ± 5°C or below and sent to the central laboratory for storage until the samples are analyzed at the direction of Allergan.

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 patients 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.

6.3.16 Pregnancy Test

Urine pregnancy testing will be performed during the screening period on females who are postmenarche prior to each treatment administration, at week 12 after each treatment, and at exit. A negative result is required prior to receiving study medication.

6.3.17 Health Outcome Measures

The PinQ is completed on day 1 prior to treatment. Both the PinQ and modified TBS are completed at weeks 6 and 12 after each treatment, and at the qualification for retreatment visit(s) (if the patient qualifies).

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]/legally authorized representative[s]) 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 legally authorized representative 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 and blood and urine sampling (supplies for central laboratory urine analysis, urine culture and sensitivity, urine dipsticks)
- patient bladder diaries
- urine collection containers
- fluid dispensing connector (for reconstitution of study drug)

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
- ultrasound for kidney and bladder assessment
- refrigerator to store dry/reconstituted study medication at a temperature of 2 to 8^{o}C, monitored by a calibrated temperature recorder
- freezer (nonfrost free) to store immunogenicity serum samples at -20 ± 5^{o}C or below, monitored by a calibrated temperature recorder
- internet connection (high-speed connection) for eCRF completion

6.5 Summary of Methods of Data Collection

An IVRS/IWRS will be used to screen, randomize, and manage the study medication inventory. Data will be collected using eCRFs via a validated electronic data capture (EDC) system. 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 primary analysis will be conducted when all BOTOX-treated patients have either: 1) qualified for retreatment, or 2) completed 48 weeks since randomization on day 1, or 3) prematurely exited prior to 48 weeks, whichever occurs sooner. All data available at the time the last patient fulfills the above requirement will be included in the primary analysis.

At the time of the primary analysis, the study will be unblinded to Allergan personnel in order to conduct the analysis and prepare the primary clinical study report. The primary analysis will support the dose recommendation for the pediatric population and will be based primarily on data from the first 12 weeks posttreatment 1. Since there will be no formal statistical hypothesis testing after the primary analysis, upon completion of the primary analysis, the investigators will then be unblinded to the patients' initial treatment assignments and the study will be unblinded from that time onwards.

The final analysis will be conducted when all patients have completed 96 weeks of study participation since randomization/day 1 or have completed a 12-week posttreatment follow-up period if their last treatment was received at week 96, or have exited the study. A detailed statistical analysis plan will be finalized prior to the first database lock, ie, at the time when the last patient fulfills the requirement for the primary analysis, as specified previously.

7.1 Analysis Populations

Two analysis populations will be used in the statistical analysis of this study: the BOTOX-treated population and the BOTOX-treated per protocol (PP) population.

The BOTOX-treated population will include all patients enrolled into the study who received at least 1 BOTOX treatment and will be used for all efficacy and safety analyses. Analyses will be based on the treatment actually received in each treatment cycle. Patients will be grouped to the nearest dose group (25 U, 50 U, or 100 U BOTOX) based on the dose actually received.

The BOTOX-treated PP population will include all randomized patients with no major protocol deviations on an as-treated basis (ie, using the dose actually received with all patients allocated to the nearest dose group [25 U, 50 U, or 100 U BOTOX]). More detailed criteria for the definition of this population will be given in the statistical analysis plan. The

list of patients excluded from the PP population will be finalized prior to the database lock. The primary efficacy variable will also be analyzed using the PP population in a sensitivity analysis.

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/legally authorized representative 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 measures:

- presence or absence of night time urinary incontinence
- number of daytime micturition episodes
- number of daytime urgency episodes
- volume voided per micturition

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 1 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 12 posttreatment 1.

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 12 after the first study treatment, missing frequencies of episodes of daytime urinary incontinence will be replaced using the last observation carried forward approach. If a patient has missing values at all scheduled posttreatment visits, the baseline value will be carried forward. No imputation will be done for missing values on visits after the posttreatment 1 week 12 visit.

7.2.2 Secondary Efficacy Variables

There are 6 secondary efficacy variables assessed at the week 12 primary timepoint:

- change from baseline in daily average frequency of daytime micturition episodes
- change from baseline in daily average frequency of daytime urgency episodes
- presence or absence of night time urinary incontinence
- volume voided per micturition
- change from baseline in PinQ total score and item scores for 3 prespecified PinQ items (worry about smell, being with friends, and feel bad about myself)
- proportion of patients with a positive treatment response on the modified TBS (ie, rating their condition “greatly improved” or “improved”)

No imputation will be done for the missing values of the secondary efficacy variables.

The presence/absence of night time urinary incontinence will be based on the response to the question asked each morning in the bladder 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 BOTOX-treated population, with imputation of missing values as described in Section 7.2.1. The primary timepoint will be week 12 after treatment 1.

For each of the BOTOX doses, descriptive statistics will be provided for the daily average frequency of normalized daytime urinary incontinence episodes at study baseline and week 12, together with the change from study baseline (arithmetic mean); the 95% confidence intervals (CI) of the arithmetic mean change will be provided.

For each of the BOTOX doses of 100 U and 50 U, the null hypothesis is that there is no difference between that dose group and the 25 U BOTOX dose group in mean change from study baseline in daily average frequency of daytime urinary incontinence episodes at week 12. The alternative hypothesis is that there is a difference in mean change from study baseline in daily average frequency of daytime urinary incontinence episodes between that BOTOX dose group and the 25 U dose group at week 12 posttreatment 1.

The hypotheses will be tested using an ANCOVA model with baseline value as covariate and treatment group as a factor.

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) 100 U versus 25 U BOTOX, and (2) 50 U versus 25 U BOTOX, treatment group differences at week 12 posttreatment 1 will be tested at the 0.05 significance level in a fixed sequence fashion. Results of hypothesis testing for 50 U versus 25 U BOTOX will be considered for statistical significance only if the treatment difference for 100 U versus 25 U BOTOX is shown to be statistically significant.

The treatment difference at week 12 posttreatment 1 in mean change from study baseline for 100 U versus 25 U BOTOX and 50 U versus 25 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

7.3.2.1 Secondary Efficacy Analyses for the Primary Efficacy Variable

A responder analysis at week 12 posttreatment 1 for daytime urinary incontinence will be performed using different thresholds of reduction from study baseline. A patient will be considered a treatment responder if they have at least a 50% reduction from study baseline at week 12 posttreatment 1 in daily average frequency of normalized daytime urinary incontinence episodes; however, other thresholds will also be evaluated.

The proportions of patients with ≥ 50%, ≥ 75%, ≥ 90%, and 100% reduction from study baseline in daily average frequency of normalized daytime urinary incontinence episodes will be presented for week 12 posttreatment 1. The difference of the proportions of patients responding between the treatment groups (100 U versus 25 U BOTOX, and 50 U versus 25 U BOTOX) will be analyzed using the CMH method controlling for baseline daytime urinary urgency incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day diary collection period).

7.3.2.2 Efficacy Analyses for the Secondary Efficacy Variables

The analysis of daytime micturition episodes, daytime urgency episodes, and volume voided per micturition at week 12 after treatment 1 will generally be analyzed as described for the primary efficacy endpoint in Section 7.3.1 except that baseline daytime urinary urgency incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day diary collection period) will be included in the ANCOVA model as an additional factor. The hierarchal testing strategy described in Section 7.3.1 will not be implemented.

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 7.3.3.9, Duration of Effect.

7.3.3 Other Efficacy Analyses

7.3.3.1 Primary and Secondary Variables at Other Timepoints During Treatment 1

The change from baseline at each scheduled visit, other than week 12 after treatment 1, in the daily average frequency of daytime urinary incontinence episodes will be analyzed in a similar way to the analyses of the primary efficacy variable at week 12 posttreatment 1, as described in Section 7.3.1; between-group comparisons will only be performed up to week 12. The proportions of responders for daytime urinary incontinence will also be analyzed for all other scheduled visits in addition to week 12.

The secondary variables at all other scheduled visits will also be analyzed as described in Section 7.3.2 for week 12 with between-group evaluations performed up to week 12 posttreatment 1.

7.3.3.2 Health Outcomes Parameters During Treatment 1

The PinQ total score and item scores for 3 prespecified items (worry about smell, being with friends, and feel bad about myself) and modified TBS questionnaire data for weeks 6 and 12 posttreatment 1 will be analyzed using either ANOVA (or ANCOVA) for continuous variables, or Pearson's chi-square test, Fisher's exact test, or CMH for categorical variables as appropriate using the BOTOX-treated population. For the modified TBS, the proportions of patients with a positive treatment response (defined as their condition either "greatly improved" or "improved") will be presented.

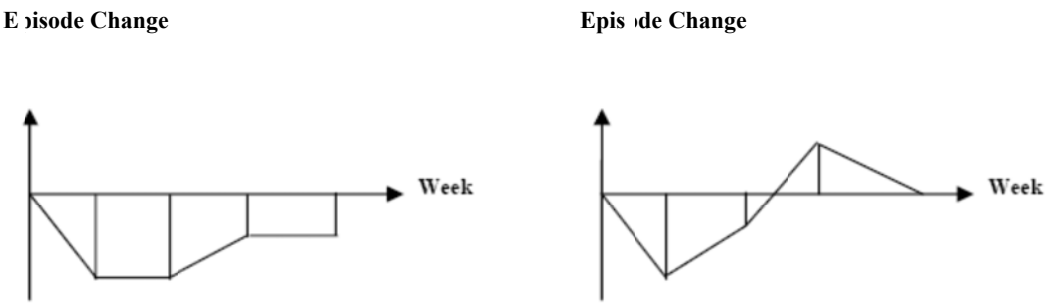
7.3.3.3 Dose-response During Treatment 1

A nonparametric analysis which evaluates the area under the curve (AUC) up to week 12 posttreatment 1 will be performed for the normalized daily average frequency of daytime urinary incontinence episodes to assess dose response.

The urinary episode change from baseline to each posttreatment visit will be derived for each patient. If the episode change is missing at an intermediate visit(s), the missing value(s) will be replaced with the average of the last nonmissing value prior to that visit and the first nonmissing value after the visit. For patients who prematurely withdraw from the study or without further observation after the visit of missing value, the change after the last visit will remain missing. The AUC of the change from baseline in urinary episode to each visit during the study will be calculated as follows for each patient. In the graph of episode change (vertical axis) versus the study visits on horizontal axis in Figure 2 below, the area

bounded by the hange curve and the horizontal axis (change = 0) will be calculated via trapezoidal method and used as a summary index fo changes across visits for each patient. A positive AUC will indicate deterioration in daytime urinary incontinence and a negative AU will indica e improvement in daytime urinary incontinenc across time.

Figure 2 Examples of AUC for Urinary Episode Change



AUC = area under the curve

For patients who prematurely withdraw from the study or without further observation after the visit of missing value, the AUC will be calculated using change up to the last visit or the last observation only.

Additional analysis exploring dose response may also be perfor ned.

7.3.3.4 Efficacy Analyses for Daytime Urinary ncontinence Episodes During Repeat Treatment(s)

For each BOTOX treatment cycle, descriptive statistics will be rovided for the daily average freq ency of normalized daytime urinary incontinence episodes at baseline and posttreatment visits. The change from study baseline (arithmetic ean) and the 95% CI of the arithmetic mea change will be provided.

A responder ana ysis for daytime urinary incontinence will be performed using different thresholds of reduction from study baseline. A patient will be c nsidered a treatment resp nder if they have at least a 50% reduction from study baseline in daily average freq ency of normalized daytime urinary incontinence; however, other thresholds will also be e aluated. T e proportion of patients with ≥ 50 , ≥ 75%, ≥ 90%, and 100% reduction from study baseline in daily average frequency of normalized daytime urinary incontinence will e presente by BOTOX treatment cycle for each posttreatment visit.

In addition, these change from baseline and responder analyses will also be conducted without the normalization of the variable to a 12-hour daytime period.

7.3.3.5 Efficacy Analyses for Daytime Micturition Episodes, Urgency Episodes, and Volume Voided Per Micturition During Repeat Treatment(s)

Analyses for daily average frequency of micturition episodes, daily average frequency of urgency episodes, and volume voided per micturition will be performed for each BOTOX treatment cycle, as described for analyses of daytime urinary incontinence episodes in Section 7.3.3.4. Responder analyses will not be performed for these variables.

7.3.3.6 Efficacy Analyses for the Presence or Absence of Night Time Urinary Incontinence During Repeat Treatment(s)

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

7.3.3.7 Health Outcomes Parameters During Repeat Treatment(s)

For the total PinQ score and item scores for 3 prespecified items (worry about smell, being with friends, and feel bad about myself), descriptive statistics of the change from baseline will be presented and the 95% CI of the mean change from baseline will be provided for each BOTOX treatment cycle at baseline and posttreatment visits.

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

7.3.3.8 Dose-response During Repeat Treatment(s)

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

7.3.3.9 Duration of Effect

Duration of treatment effect will be assessed as time from each study drug administration to a) request for retreatment and b) qualification for retreatment using a Kaplan-Meier survival

analysis. The time from the day of each BOTOX treatment to the request for the subsequent treatment will be estimated using the Kaplan-Meier survival method for each treatment group for each BOTOX treatment cycle. For those patients who did not request retreatment, their data will be censored using the date of their last study visit or study exit. The proportions of patients/parents/legally authorized representatives requesting retreatment in each BOTOX treatment cycle will also be presented. In addition, time to qualification for retreatment will be presented and analyzed as described above for time to request for retreatment.

7.3.4 Safety Analyses

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

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

Data will be presented by BOTOX treatment cycle and grouped according to the actual dose received at that treatment cycle (grouped to the nearest dose group [25 U, 50 U, or 100 U BOTOX]), as well as by an overall BOTOX group (ie, regardless of dose).

As described in Section 6.3.15, immunogenicity samples will be analyzed using a 2-step process (toxin-binding and toxin-neutralizing antibodies). Results from both steps will be presented.

7.4 Sensitivity Analysis

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

In addition, for the BOTOX-treated population, 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.

7.5 Subgroup Analyses

For each BOTOX treatment cycle, descriptive statistics will be provided for the daily average frequency of daytime urinary incontinence episodes presented by investigator site, as well as by key demographic or baseline characteristics, including baseline daytime urinary urgency incontinence episodes (a total of ≤ 6 episodes or > 6 episodes over the 2-day diary collection period), race, and sex.

7.6 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, 191622-095 and 191622-520. The mean (standard deviation [SD]) of the change from baseline in daily urinary incontinence at week 12 was -2.65 (3.33) and -2.95 (3.58) in Studies 191622-095 and 191622-520, respectively.

Approximately 36 patients per treatment group are to be enrolled for the study. This includes 32 patients per treatment group and an increase to 36 per group in order to address patient attrition (estimated to be 10% by week 12).

Table 2 displays the estimated difference between 100 U BOTOX (maximum 6 U/kg) and 25 U BOTOX (maximum 6 U/kg) in mean daily average frequency of daytime episodes of urinary incontinence change from baseline at week 12 for a range of common SDs. All calculations assume 32 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 (Statistical Solutions Ltd., Cork, Ireland), and the CI for the difference of 2 means based on normal distribution.

Table 2 Sample Size Calculation

Standard Deviation	Distance From Mean to the Limit
2.0	0.980
2.5	1.225
3.0	1.470
3.5	1.715
4.0	1.960

Note: The ranges of the SDs are determined based on the values from the adult pivotal phase 3 OAB studies, 191622-095 and 191622-520. The estimate of the SD for the 100 U BOTOX treatment group is 3.33 for Study 191622-095, 3.58 for Study 191622-520, and 3.46 for the 2 studies combined. The distance from mean to limit indicates how much the CI for the mean extends from the observed difference in means in either direction.

7.7 Interim Analyses

Other than the primary analysis described in Section 7 no interim analyses are planned.

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 prior to any study-related procedures or change in treatment. The patient 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 that 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 the randomization/day 1 visit to confirm that patient bladder diary records support protocol requirements for urinary urgency incontinence. In addition, prior to randomization, the investigator should confirm that all “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, see (Schedule of Visits and Procedures). 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. During the study, every effort should be made to perform the study procedures as indicated in Table 1.

8.4 Instructions for the Patients

Patients/parents/legally authorized representatives 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 during the study whenever possible
- to strictly follow instructions provided by the investigator if CIC is deemed necessary
- to change wet underwear/pads/diapers 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
- to complete and bring diaries 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/legally authorized representatives) 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/legally authorized representatives 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 provided to Allergan and 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/legally authorized representative is unwilling or unable to continue to comply with study procedures
- investigator requests a dose increase after the patient has received 2 treatments with 100 U BOTOX

- investigator assesses that the patient should not be retreated with the current dose, but that a dose reduction would be warranted

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

Adverse events occurring during the study will be recorded on an adverse event eCRF. If adverse events occur, the first concern will be the safety of the study participants.

9.1 Definitions

9.1.1 Adverse Event

An adverse event is 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 OAB, 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 has been obtained). At each visit, the investigator will begin by querying for adverse events by asking each patient 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 Study-specific Definitions for Particular Adverse Events

Definition of Adverse Event of Urinary Retention:

An adverse event of urinary retention should only be recorded when a patient has a raised PVR that requires intervention with CIC according to the following criteria:

- patient has a PVR of ≥ 350 mL (regardless of symptoms), OR
- patient has a PVR ≥ 200 mL and < 350 mL and the patient reports associated symptoms ie, sensation of bladder fullness or inability to void despite persistent effort, that in the investigator's opinion require CIC.

Definition of Adverse Event of Residual Urine Volume:

An adverse event of residual urine volume should be recorded if, in the investigator's opinion, the raised PVR is clinically significant but does not fulfill the above definition for urinary retention.

Definition of Adverse Event of Urinary Tract Infection

An adverse event of UTI will be recorded if both the following criteria are fulfilled, regardless of patient symptoms:

- a positive urine culture result with a bacteriuria count of > 10^5 CFU/mL
- leukocyturia of > 5/hpf

If a patient meets the criteria for the definition of a UTI, the investigator will record whether the UTI was "symptomatic" or "asymptomatic" on the adverse event eCRF

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

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 patient 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.

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

Any pre-planned 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 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 Sheet 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 the sponsor 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 email 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 protocol.

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 Unmasking of Study Medication

When necessary for the safety and proper treatment of the patient, the investigator can unmask the patient's treatment assignment to determine which dosage of BOTOX has been

assigned and institute appropriate follow-up care. When possible, the sponsor (Allergan Medical Safety Physician) should be notified prior to unmasking study medication. The investigator should inform the sponsor (Allergan Medical Safety Physician) of the unmasking if there is no notification prior to the unmasking.

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 Patients

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

Written informed consent is to be obtained from each patient and/or from the patient's legally authorized representative prior to initiating any study-related activities or procedures. 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/legally authorized representative 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 and 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 patient'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 following:

- to publish anonymous patient data from the study; and
- to create and maintain a data repository

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, 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 entered into the patient's medical record:

- patient's name
- patient's contact information
- study title and/or the protocol number of the study and the name of Allergan
- a statement that informed consent and/or assent, was obtained (including the date). A statement that written authorization (US sites only), data protection consent (EU sites only), or other country and local patient privacy required documentation for this study has been obtained (including the date)
- date that the patient was randomized into the study, patient number, patient medication kit number, and date and details of study drug administration
- dates of all patient visits and date of any request for retreatment
- reason for dose option
- medical and surgical history (including prior medications for treatment of OAB)
- 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)
- all concurrent procedures performed during the study
- occurrence and status of any adverse events (including any procedure-related adverse events)

- PVR urine volumes
- reason, if applicable, de novo CIC not discontinued in accordance with criteria stated in Section 6.3.9 Post-void Residual Urine Volume
- results of bladder and kidney ultrasound
- results of laboratory tests performed by the site (eg, results of urine pregnancy tests, urine dipstick)
- results of laboratory tests performed by the central laboratory
- vital signs and physical examination findings
- height and weight
- date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation

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
- PinQ
- modified TBS

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

10.4.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each patient's eCRFs and related documents. An investigator who has signed the protocol signature page should personally sign for the eCRFs (as indicated in the eCRFs) to ensure that the observations and findings are recorded on the case report forms correctly and completely. The eCRFs are to be submitted to Allergan in a timely manner at the completion of the study, 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, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of CRFs 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

10.5.1 Labeling/Packaging

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

10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units (ie, number of vials) received from Allergan, dispensed to the patients, and the number of units returned to Allergan 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 an appropriately qualified person to patients in the study. The medication is to be used in accordance with the protocol and under the direct supervision of an investigator.

10.5.3 Return or Disposal of Study Medications and/or Supplies

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

10.6 Monitoring by the Sponsor

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

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

10.7 Handling of Biological Specimens

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

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

Allergan shall have full ownership rights to any biological specimens/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 investigator(s) and sites 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 for the primary and final analyses.

11. References

Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology of the lower urinary tract function: Report for the Standardisation Sub-committee of the International Continence Society. Neurourol Urodynam. 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;174:977–82; discussion 982–983.

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.

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;5:319–328.

Chapple C, Sievert KD, MacDiarmid S, Khullar V, Radziszewski P, Nardo C, et al. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2013 Apr 10. pii: S0302-2838(13)00355-2. doi: 10.1016/j.eururo.2013.04.001. [Epub ahead of print].

Coelho A, Dinis P, Pinto 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.

Fitzgerald MP, Thom DH, Wassel-Fyr C, Subak L, Brubaker L, Van Den Eeden SK et al. Childhood urinary symptoms predict adult overactive bladder symptoms. J Urol. 2006;175:989-993.

Franco I. Overactive bladder in children. Part 1: pathophysiology. J Urol. 2007;178:761-768.

Franco I. Pediatric overactive bladder and lower urinary tract dysfunctions: diagnosis and treatment. Ped Health. 2008;2(2):189-203.

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 literature review. J Pediatr Urol. 2009;5:156–164.

Hoebeke P, De Caestecker K, Vande Walle J, Dehoorne J, Raes A, Verleyen P, et al. The effect of botulinum-A toxin in incontinent children with therapy resistant overactive detrusor. J Urol. 2006;176:328-331.

Lubsen J, Kirwan BA. Combined endpoints: can we use them? Stat Med. 2002;21(19):2959-2970.

Marschall-Kehrel D, Feustel C, Persson de Geeter C, Stehr M, Radmayr C, Sillén U, et al. Treatment with propiverine in children suffering from nonneurogenic overactive bladder and urinary incontinence: results of a randomized placebo-controlled phase 3 clinical trial. Eur Urol. 2009;55(3):729-736.

Marte A, Borrelli M, Sabatino MD, Balzo BD, Prezioso M, Pintozzi L, et al. Effectiveness of botulinum toxin-A for the treatment of refractory overactive bladder in children. Eur J Pediatr Surg. 2010;20:153-157.

Minassian VA, Lovatsis D, Pascali D, Alarab M, Drutz HP. Effect of childhood dysfunctional voiding on urinary incontinence in adult women. Obstet Gynecol. 2006;107:1247-1251.

Mosteller RD. Simplified calculation of body-surface area. N Eng J Med. 1987;317(17):1098.

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.

Nijman RJ, Borgstein NG, Ellsworth P, Djurhuus JC. Tolterodine treatment for children with symptoms of urinary urge incontinence suggestive of detrusor overactivity: results from 2 randomized, placebo controlled trials. J Urol. 2005;173(4):1334-1339.

Nitti VW, Dmochowski R, Herschorn S, Sand P, Thompson C, Nardo C, et al; EMBARK Study Group. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. J Urol. 2013;189:2186-2193.

Ruarte AC, Quesada EM. Urodynamic evaluation in children. In: Retik AB, Cukier J, editors. International perspectives in urology (14). Pediatric urology. Baltimore:Williams and Wilkins;1987. p. 114-32.

Sager C, Burek C, Durán V, Corbetta JP, Weller S, Juan B, et al. Pharmacotherapy in pediatric neurogenic bladder intravesical botulinum toxin type a. ISRN Urol. 2012;2012:763159:1-6.

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 Paediatric Urology. European Society for Paediatric Urology. 2012;1-114.

Van Arendonk KJ, Austin JC, Boyt MA, Cooper CS. Frequency of wetting is predictive of response to anticholinergic treatment in children with overactive bladder. Urology. 2006;67(5):1049-1053.

12. Attachments

12.1 Preparation of Study Medication

12.2 Study Treatment Injection Pattern

12.3 Total Volume Voided Collection

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

12.5 Package Insert

12.6 Glossary of Abbreviations

12.7 Protocol Amendment Summary #1

12.8 Protocol Amendment Summary #2

12.1 Preparation of Study Medication

Study medication vials will be reconstituted for the 25 U, 50 U, and 100 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 Pharmacy Manual.

12.1.1 BOTOX 25 U (not to exceed 6 U/kg)

Body Weight		Volume of saline (diluent) to add to vial for reconstitution (mL)	Volume of reconstituted study medication and saline to draw into dosing syringe (mL)		Final volume in dosing syringe (mL)	Final concentration in dosing syringe (U/mL)	Final dose of BOTOX in syringe
kg	lbs		Study medication	Saline			
≥ 14	≥ 31	5.0	1.25	8.75	10.0	2.5	25 U

12.1.2 BOTOX 50 U (not to exceed 6 U/kg)

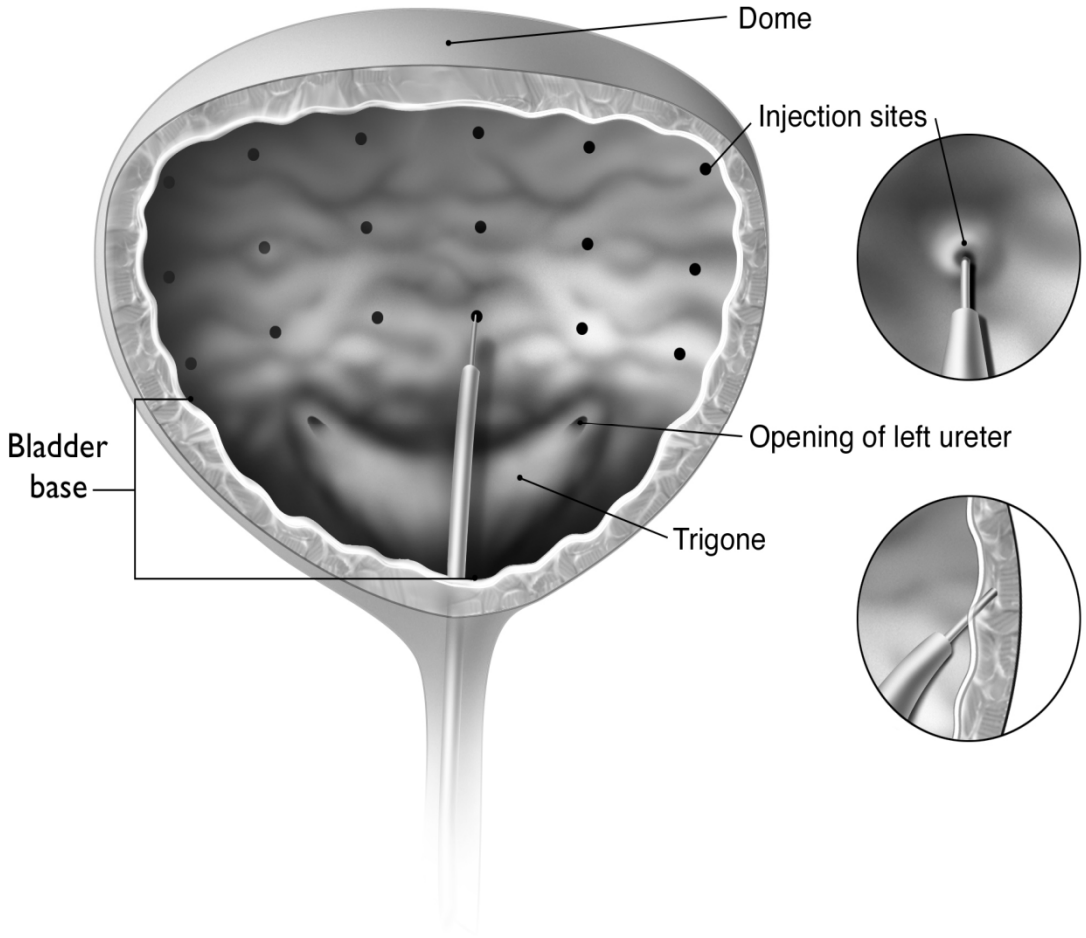
Body Weight		Volume of saline (diluent) to add to vial for reconstitution (mL)	Volume of reconstituted study medication and saline to draw into dosing syringe (mL)		Final volume in dosing syringe (mL)	Final concentration in dosing syringe (U/mL)	Final dose of BOTOX in syringe
kg	lbs		Study medication	Saline			
≥ 14	≥ 31	5.0	2.5	7.5	10.0	5.0	50 U

12.1.3 BOTOX 100 U (not to exceed 6 U/kg)

Body Weight		Volume of saline (diluent) to add to vial for reconstitution (mL)	Volume of reconstituted study medication and saline to draw into dosing syringe (mL)		Final volume in dosing syringe (mL)	Final concentration in dosing syringe (U/mL)	Final dose of BOTOX in syringe
kg	lbs		Study medication	Saline			
14 to < 16	≥ 31 to < 35	5.0	4.2	5.8	10.0	8.4[a]	84 U[a]
16 to < 18	≥ 35 to < 40	5.0	4.8	5.2	10.0	9.6[a]	96 U[a]
≥ 18	≥ 40	5.0	5.0	5.0	10.0	10.0[a]	100 U[a]

[a] Based on lowest weight in range

12.2 Study Treatment Injection Pattern



12.3 Total Volume Voided Collection

Supplies:

- bladder diary
- urine collection containers

Schedule:

Collected over one daytime period (waking hours) during the 2-day bladder diary collection during screening and prior to each posttreatment visit.

Preparation:

All patients will use a bladder diary to record their daytime total volume voided data. Patients will measure their urine each time they void during the day (voluntary and catheterization as appropriate). Prior to receiving their bladder diary, patients will be trained by the site on the use of the diary and the data to be collected.

The site will provide the patient with the required urine collection containers. This container should be used to measure each void during the daytime period.

On the day that the patient selects to collect their daytime volume voided, they should adhere to the recommended daily fluid intake indicated to them by the investigator at the time they enter the study.

The patient will be instructed to clean the urine collection container after each void. This is to avoid contamination. In addition, the patient should understand that in order to record accurate data they must ensure that the urine collection container is empty and dry prior to each use.

The patient will be instructed to measure the volume of each void as it occurs and enter the amount into their diary. The patient will be instructed to place the urine collection container on a flat surface prior to recording the urine volume to ensure the measurement is recorded accurately. The patient should record the time and the amount of urine voided as soon as possible after each void.

The patient will be instructed to begin collecting urine with the first urination of the day (first morning void) and to collect and measure urine up to and including their last void before going to bed.

The site must instruct the patient NOT to estimate the measurements if the urine collection container is not used, although the patient should record all other diary information required for the void. The patient should resume measuring at the next void.

If patient's visit day is rescheduled, the study coordinator must ensure adequate time has been provided for the patient to record 2 diary data days including 1 daytime total volume voided collection in the week prior to the rescheduled visit.

If the total volume voided collection is not performed, the patient should contact the site immediately. If the patient does not complete the daytime total volume voided procedure, the site must notify Allergan. Detailed instructions on the total volume voided collection procedure are also outlined in the Study Manual.

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

Patient questionnaires will be:

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

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

Pediatric Incontinence Questionnaire (PinQ)

The PinQ is a 20-item questionnaire completed by the patient which was developed and validated in children with bladder dysfunction. The PinQ was designed to assess the impact of bladder problems from the child's perspective (Bower et al, 2006). It has also been validated for completion by parents/legally authorized representative s when patients can not complete it themselves (Bachmann et al, 2009). The questionnaire can be completed by patients, parents, or legally authorized representatives and this will be indicated on the questionnaire.

Patients/parents/legally authorized representatives are asked to respond to questions about how the patient felt during the past 7 days.

The patient/parent/legally authorized representative will respond to each of the following 20 questions with one of 5 categorical responses ("no", "hardly ever", "sometimes", "often", or "all of the time"):

1. *I get shy because of my bladder problems*
2. *People in my family treat me in a different way because of my bladder problem*
3. *I am worried that my clothes smell of wee*
4. *I think that my bladder problem won't get better*
5. *Mum and dad worry about me because of my bladder problem*
6. *I would feel better about myself if I didn't have a bladder problem*
7. *My bladder problem makes me feel nervous*
8. *Mum or dad sometimes seem a bit cranky because of my bladder problem*
9. *My bladder problems stop me from going on sleep-overs or holiday*
10. *My bladder problem makes me feel bad about myself*
11. *I wake up during my sleep because of my bladder problems*
12. *I miss out on doing things because of my bladder problem*
13. *I feel unhappy because of my bladder problems*
14. *My bladder problem makes me feel sad*
15. *I think about my bladder problems when choosing which sport to play*
16. *I have to go to the toilet when I'm watching a movie*
17. *If my bladder problem was fixed, I would invite more friends to the house*
18. *I choose hobbies that won't be spoiled by stopping to go to the toilet*
19. *My bladder problems make me feel different to other people*
20. *I miss out on being with friends because of my bladder problem*

Modified Treatment Benefit Scale (Modified TBS)

The TBS is single-item scale designed to assess the change in the patient's OAB condition following treatment (Colman et al, 2008). The patient's current condition (urinary problems, urinary incontinence) is compared to their condition prior to receipt of any study treatment. The questionnaire can be completed by patients, parents, or legally authorized representatives, and this will be indicated on the questionnaire.

Patients/parents/legally authorized representatives respond to the following:

Please write down what you think about your current condition (urinary problems such as sudden need to pee/short warning time, and/or leaking urine or pee) compared to your conditon ***before you received any study treatment in this trial.***

My condition has

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

since I had any study treatment.

12.5 Package Insert

The appropriate package insert(s)/Summary of Product Characteristics will be supplied to investigators in countries where the product is marketed.

12.6 Glossary of Abbreviations

Term/Abbreviation	Definition
ANOVA	analysis of variance
ANCOVA	analysis of covariance
AUC	area under the curve
BOTOX®	Botulinum Toxin Type A Purified Neurotoxin Complex (US Adopted Name is OnabotulinumtoxinA)
BSA	body surface area
BUN	blood urea nitrogen
CFU	colony forming units
CI	confidence interval
CIC	clean intermittent catheterization
CMH	Cochran-Mantel-Haenszel
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
FDA	Food and Drug Administration
GCP	Good Clinical Practices
eGFR	estimated glomerular filtration rate
HIPAA	Health Insurance Portability and Accountability Act
hpf	high powered field
HRQOL	health-related quality of life
ICH	International Conference on Harmonisation
IDR	independent drug reconstitutor
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
kDa	kilodalton
OAB	overactive bladder
PinQ	Pediatric Incontinence Questionnaire
PP	per protocol
PVR	post-void residual
RBC	red blood cell

SD	standard deviation
TBS	Treatment Benefit Scale
TRPV1	transient receptor potential vanilloid 1
unit (U)	one unit (U) of BOTOX® corresponds to the calculated median lethal dose (LD_{50}) in mice of the reconstituted BOTOX® injected intraperitoneally
US	United States
UTI	urinary tract infection
WBC	white blood cell

12.7 Protocol Amendment Summary #1

Title: BOTOX® in the Treatment of Urinary Incontinence Due to Overactive Bladder in Patients 12 to 17 Years of Age

Protocol 191622-137 Amendment 1

Date of Amendment: February 2014

Amendment Summary

In this amendment, additional clarification has been added in Section 5.5 (Method for Assignment to Treatment Groups/Randomization) and Section 7 (Statistical Procedures).

The wording of Section 8.7 (Early Discontinuation of Patients) has been aligned with recent protocols within the Urology Therapeutic Area at Allergan.

This amendment represents the initial protocol for use in this study.

12.8 Protocol Amendment Summary #2

Title: BOTOX® in the Treatment of Urinary Incontinence Due to Overactive Bladder in Patients 12 to 17 Years of Age

Protocol 191622-137 Amendment 2

Date of Amendment: September 2014

Amendment Summary

This summary includes the main changes made to the Protocol 191622-137 Amendment 1 (February 2014).

Section	Revision	Rationale
Protocol Summary; Section 4.4 – Exclusion Criteria	Addition of an exclusion criterion regarding medical conditions that may put patients at increased risk with exposure to BOTOX.	Additions/clarifications in response to a Health Authority request
Protocol Summary; Section 4.4 – Exclusion Criteria	The wording of exclusion criteria regarding history or evidence of any pelvic or urological abnormalities has been clarified to include further examples (ie, clinically relevant vesicoureteric reflux or disease of the bladder) and reconstructive surgery (ie, bladder augmentation).	Additions/clarifications in response to a Health Authority request
Protocol Summary; Section 4.4 – Exclusion Criteria	Addition of exclusion criterion regarding medical conditions (hemophilia, or other clotting factor deficiencies, or disorders that cause bleeding diathesis)	Patient safety

Protocol Summary; Section 4.4 – Exclusion Criteria	Addition of exclusion criterion regarding patients who cannot withhold any antiplatelet, anticoagulant therapy, or other medications with anticoagulant effects for 3 days prior to randomization/day 1.	Patient safety

The following is a summary of other content-oriented changes that were made, together with a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section	Revision	Rationale
Protocol Summary	Aligned criteria for primary analysis to be consistent with Section 7 (Statistical procedures)	Consistency and clarification
Protocol Summary; Section 7.6 – Sample Size Calculation	Clarified that the CI for the difference of 2 means was based on normal distribution for the purpose of the sample size calculation	Clarification
Protocol Summary; Section 4.4 – Exclusion Criteria; Section 4.5.2 – Prohibited Medications/Treatments	Clarified the usage of medications for nocturia/nocturnal enuresis (ie, desmopressin) and other medications for OAB (eg, mirabegron) and their washout periods.	Clarification
Section 4.4 – Exclusion Criteria	Clarified exclusion criterion regarding usage of psychiatric medications or medications for attention deficit hyperactivity to indicate that patients need to have been on a stable dose prior to study entry rather than for 6 months prior.	Clarification

Section	Revision	Rationale
Section 5.9.1 – Day of Treatment Criteria	Added criterion regarding PVR urine volume to be < 200 mL for patients to qualify for retreatment. (previously this was only mentioned in Section 5.10.1).	Clarification
Section 5.10.1 – Qualification for Retreatment Criteria	Clarified that the PVR value obtained at qualification for retreatment must be confirmed to have been < 200 mL for the "day of treatment criteria" to be met.	Clarification
Table 1; Section 6.3.13 – Urinalysis, Culture, and Sensitivity	Clarified that the urinalysis, culture, and sensitivity procedures are to be performed at all clinic visits.	Clarification
Section 6.4	Added fluid dispensing connector (for reconstitution of study drug) to other study supplies.	Clarification
Section 7.2.1 – Primary Efficacy Variable	Clarified that if a patient has missing values at all scheduled posttreatment visits, the baseline value will be carried forward	Clarification
Section 9.1.1 – Adverse Event	Clarified that events considered to be either new or worsening of anticipated clinical signs or symptoms collected as clinical efficacy variables and related to the underlying disease of OAB should not be collected adverse events unless the disease progression is greater than anticipated in the natural course of the disease.	Added as per the current Allergan Protocol Template