NCT03320850

Study ID: 1839-201-021

Title: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Single-treatment, 2-stage, Dose-finding Study Evaluating the Efficacy and Safety of BOTOX® Intravesical Instillation in Participants With Overactive Bladder and Urinary Incontinence

Protocol Amendment 2 Date: 20Dec2018

Title Page

Protocol Title: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Single-treatment, 2-stage, Dose-finding Study Evaluating the Efficacy and Safety of BOTOX® Intravesical Instillation in Participants with Overactive Bladder and Urinary Incontinence

Amendment Number: 2

Brief Protocol Title: BOTOX® Intravesical Instillation in Participants with Overactive Bladder and Urinary Incontinence

Product: BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex (US Adopted Name is onabotulinumtoxinA)

Sponsor Name and Legal Registered Address: Allergan (North America), 2525 Dupont Drive, Irvine, California USA, 92612

Regulatory Agency Identifying Number(s): Investigational New Drug (IND) number [redacted]

Emergency Telephone Number: Refer to the study contacts page

SAE Reporting Fax Number/Email:

Business Unit /Legacy Organization	Email	Fax
Allergan Pharmaceuticals	[redacted]	[redacted]

Sponsor Signatory:

[redacted]
Vice President and Therapeutic Area Head
Internal Medicine, Women's Health, Anti-Infectives and Urology

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

Protocol Amendment Summary of Changes Table

Document History	
Document	**Date**
Amendment 2	20 Dec 2018
Amendment 1	30 August 2017
Original Protocol	8 June 2017

Amendment 2 (20 Dec 2018)

Overall Rationale for the Amendment:

[redacted]

Section	Revision	Summary
Protocol Title Page	Sponsor signatory changed	Update due to change in sponsor signatory
1. Synopsis	Location of study sites changed from North America and Europe to North America and Canada	Updated location of study
[redacted]		
6.2. Exclusion Criteria, 1.03	Implanted electrostimulation/ neuromodulation devices must be inactive 4 weeks prior to screening diary instead of randomization/Day 1	Clarified language to ensure no effects from the device are remaining during the diary completion period

6.2. Exclusion Criteria, 1.07	Specified exclusionary PSA level limits are to be determined from screening lab results	Clarified language
6.2. Exclusion Criteria, 2.01	Defined "therapies" as non-pharmacotherapies for OAB and specified initiation of non-pharmacotherapies for OAB are not to be initiated during the trial	Clarified language
7.1. Treatments Administered	[redacted]	
7.3. Method of Treatment Assignment	Removed language, "At the time of randomization, participants will be assigned a randomization number. Numbers should be assigned in ascending order and must not be omitted or reused."	Updated per changes to company procedures
7.5. Preparation/Handling/Storage/ Accountability	[redacted]	Corrected storage temperature for Hydrogel
7.7.3. Prohibited Treatments During the Study	Defined "therapies" as non-pharmacotherapies for OAB and specified initiation of non-pharmacotherapies for OAB are not to be initiated during the trial	Clarified language

[redacted]

Approval Date: 20-Dec-2018

[redacted]

9.2.6. Study-Specific Definitions for Particular Adverse Events	Added, "If a patient has symptomatic leucocyturia and/or symptomatic bacteriuria but does not meet the above criteria for a UTI, "symptomatic leucocyturia" and/or "symptomatic bacteriuria" are recorded individually as adverse events and the symptoms (e.g. dysuria) are reported separately as well."	Provided additional guidance on how to record events that do not meet the protocol-defined adverse event of UTI
[redacted]		

[redacted]

[redacted]

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1. Synopsis

Protocol Title: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Single-treatment, 2-stage, Dose-finding Study Evaluating the Efficacy and Safety of BOTOX® Intravesical Instillation in Participants with Overactive Bladder and Urinary Incontinence

Protocol Number: 1839-201-021

Brief Title: BOTOX® Intravesical Instillation in Participants with Overactive Bladder and Urinary Incontinence

Study Rationale:

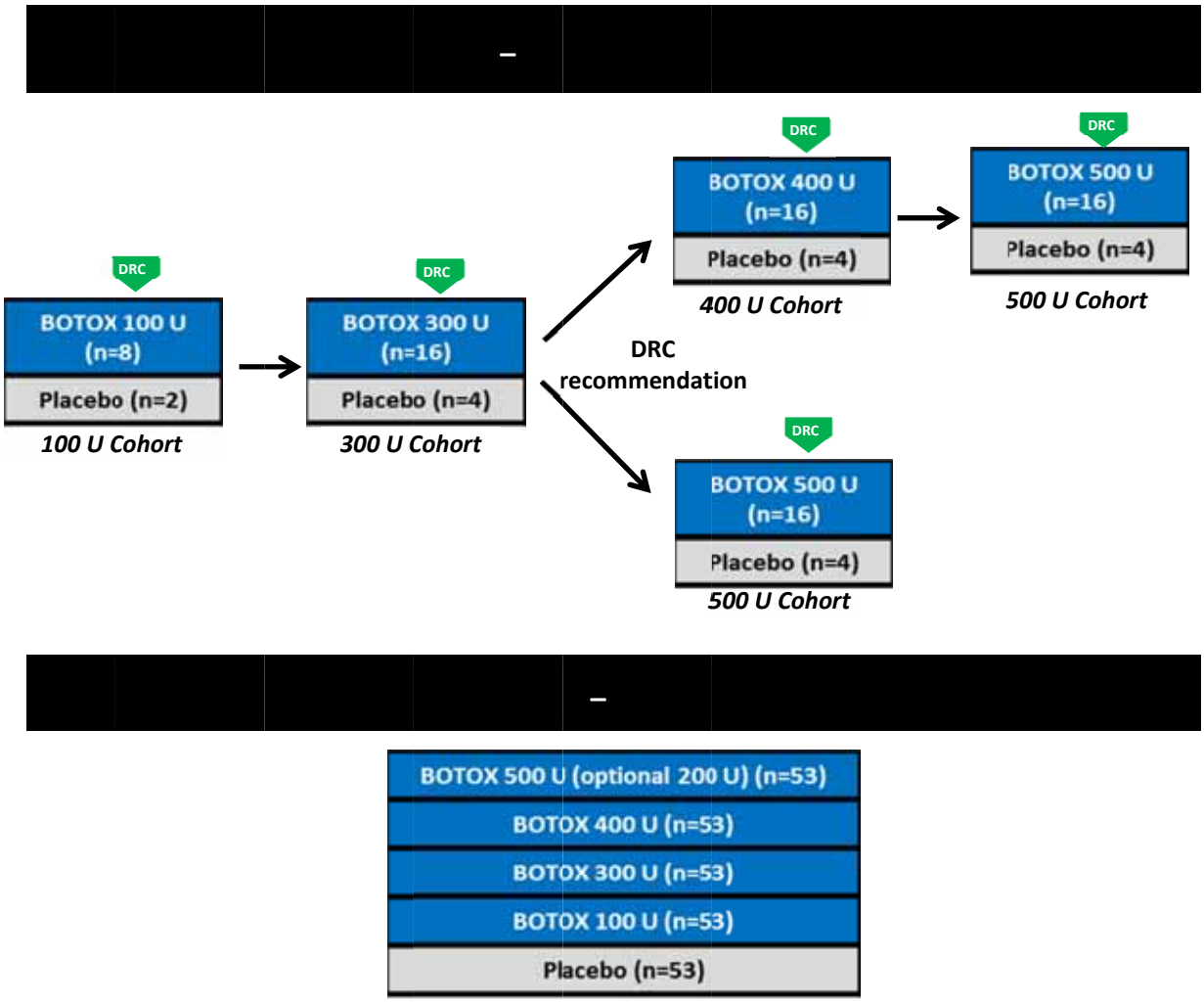
For patients with overactive bladder (OAB) and urinary incontinence who are inadequately managed by pharmacologic therapies, or are not suitable candidates for more invasive therapies, there is an unmet medical need for a less invasive, more convenient OAB treatment option. Study 1839-201-021 will investigate the efficacy and safety of BOTOX administered via intravesical instillation (BOTOX and Hydrogel [RTGel™] admixture) which will eliminate the need for cystoscopy to administer the treatment, as well as eliminate the need for prophylactic antibiotic use, and for local anesthesia of the bladder prior to administration. The results of Study 1839-201-021 will be used to determine the efficacious and safe dose for future investigation in phase 3 clinical trials.

Objectives and Endpoints:

Objectives	Endpoints
• To compare the efficacy of a single treatment of BOTOX intravesical instillation, with possible doses ranging from 100 U up to 500 U, with placebo in participants with OAB and urinary incontinence	Primary Endpoint: • change from baseline at Week 12 (Stage 2) in the average number of urinary incontinence episodes per day Secondary Endpoint: • change from baseline at Week 12 (Stage 2) in the average number of micturition episodes per day • change from baseline at Week 12 (Stage 2) in the average volume voided per micturition
• To compare the safety of a single treatment of BOTOX intravesical instillation, with possible doses ranging from 100 U up to 500 U, with placebo in participants with OAB and urinary incontinence	• Adverse events, physical examination, vital signs, urine dipstick reagent strip test, urinalysis (with urine culture/sensitivity, as applicable), hematology and clinical chemistry, post-void residual (PVR) urine volume, kidney and bladder ultrasound, urine pregnancy test for women of childbearing potential, concomitant medications, concurrent procedures

Overall Study Design:

- Type of Design: Multicenter, randomized, double-blind, placebo-controlled, single-treatment, 2-stage, dose-finding study; Stage 1 is a placebo-controlled, dose escalation design with 3 or 4 consecutive cohorts and Stage 2 is a 5-arm, placebo-controlled, parallel-group design.



[a] Up to 4 consecutive cohorts are planned for investigation in Stage 1; the decision to dose escalate to 300 U, possibly 400 U, and 500 U Cohorts will be based on independent Data Review Committee (DRC) review of unblinded safety data when all participants reach Week 6 in the previous cohort. After safety review of the 300 U cohort, the DRC will recommend whether to proceed with dose escalation either to BOTOX 400 U followed by BOTOX 500 U or whether it is safe to proceed directly to BOTOX 500 U.

[b] Stage 2 will begin after confirmation of the 4 BOTOX doses for investigation in Stage 2 based on unblinded review of safety results from the 500 U Cohort in Stage 1 by the DRC

- Population: Participants with OAB and urgency urinary incontinence who have an inadequate response to or are intolerant of pharmacologic therapy. (Note: Pharmacologic therapies are oral or transdermal, therapies approved in the treatment of OAB.) Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 6.1 and 6.2 of the protocol.

- Study Treatment Groups:

  Stage 1:

  - 100 U Cohort: 100 U BOTOX intravesical instillation (BOTOX and Hydrogel admixture)
  - 300 U Cohort: 300 U BOTOX intravesical instillation (BOTOX and Hydrogel admixture)
  - 400 U Cohort (optional): 400 U BOTOX intravesical instillation (BOTOX and Hydrogel admixture)
  - 500 U Cohort: 500 U BOTOX intravesical instillation (BOTOX and Hydrogel admixture)

  Based on the observed safety data from the 100 U and 300 U Cohorts, the Data Review Committee (DRC) will recommend to proceed with either BOTOX 400 U followed by BOTOX 500 U or whether it is safe to dose escalate directly to BOTOX 500 U.

  Stage 2:

  Four doses of BOTOX will be investigated in parallel treatment groups as shown below. Depending on the outcome of DRC review of safety results from the 500 U Cohort in Stage 1, BOTOX 500 U may be replaced with a BOTOX 200 U treatment group.

  - 100 U BOTOX intravesical instillation (BOTOX and Hydrogel admixture)
  - 300 U BOTOX intravesical instillation (BOTOX and Hydrogel admixture)
  - 400 U BOTOX intravesical instillation (BOTOX and Hydrogel admixture)
  - 500 U BOTOX (option to replace with 200 U) intravesical instillation (BOTOX and Hydrogel admixture)

- Controls:

  Stage 1 and Stage 2: Placebo intravesical instillation (BOTOX placebo and Hydrogel admixture)

- Dosage/Dose Regimen:

  - For each participant in Stage 1 or Stage 2, a single treatment will be administered on Day 1 following fulfillment of the "day of treatment criteria" according to the treatment groups outlined above.

  - Study treatment will be administered as a single intravesical instillation through a sterile, single-use transurethral catheter using aseptic technique as per local site practice. A total volume of 60 mL of study treatment (BOTOX or placebo and Hydrogel admixture) will be instilled into the bladder. Subsequently, the transurethral catheter will be flushed with normal saline at room temperature (~1.5 mL saline for females and ~3.0 mL saline for males) to ensure delivery of the small amount of study medication remaining in the catheter.

  - After treatment administration, participants will be instructed to hold the instilled study treatment for 60 minutes (or as long as possible, if less than 60 minutes) and remain in the clinic during this time. During the first 30 minutes, participants will be kept in a supine or sitting position. The time and volume of the participant's first void post-instillation as well as the time to last visualization of BOTOX (or placebo) and Hydrogel admixture in voided urine post-instillation will be recorded.

- Randomization/Stratification:

  - Participants will be enrolled at clinical study sites into 1 of 2 stages. Initially, approximately 50 to 70 participants will enter Stage 1 and be enrolled into one of the dose escalation cohorts (10 participants in the 100 U Cohort and 20 participants in each of the remaining cohorts). Each cohort in Stage 1 will be randomized separately and enrollment will be sequential, starting with the 100 U Cohort (BOTOX 100 U or placebo). After review of the safety data from the 500 U Cohort of Stage 1 by the DRC, sites will be notified that enrollment into Stage 2 may begin. Approximately 265 participants will be enrolled into Stage 2 and randomized into 1 of 5 parallel

treatment groups, including 4 BOTOX arms and 1 placebo arm. Participants who receive study treatment in Stage 1 are not eligible to enroll in Stage 2.

- At Day 1, participants in both Stage 1 and Stage 2 will be randomized centrally to receive either a single treatment of BOTOX or matching placebo via intravesical instillation. Randomization will be stratified by baseline urgency urinary incontinence episodes and sex for Stage 2 only.

- In Stage 1, participants will be randomized in a 4:1 ratio to receive either BOTOX (100 U, 300 U, 400 U [optional], 500 U) or placebo. For each cohort in Stage 1, an unblinded safety review by the DRC will be performed when all participants reach Week 6. Enrollment into the next cohort at the higher dose will begin only after the DRC has deemed it safe to proceed to the next cohort.

- In Stage 2, participants will be randomized in a 1:1:1:1:1 ratio for treatment with either BOTOX 100 U, BOTOX 300 U, BOTOX 400 U, BOTOX 500 U (or 200 U), or placebo.

- Confirmation of the BOTOX doses for investigation in Stage 2 will occur after review of unblinded safety data from the 500 U Cohort in Stage 1 by the DRC. Based on this review, the DRC will have the option to replace the BOTOX 500 U treatment group with BOTOX 200 U in Stage 2.

- Visit Schedule:

[redacted]

[redacted]

Number of Participants:

Approximately 70 to 100 participants will be screened to randomize ~50 to 70 participants to study treatment in Stage 1. Approximately 380 participants will be screened to randomize ~265 participants to study treatment in Stage 2.

Number of Sites:

Stage 1: Approximately 25 sites in the United States

Stage 2: Approximately 65 sites in The United States and Canada

Treatment Groups and Study Duration:

Refer to section on Overall Study Design above for treatment group information. Participation in Stage 1 will be a total of 14 weeks (2-week screening and 12-week treatment/follow-up period) or, if participating in Stage 2, will be a total of 28 weeks (4-week screening and 24-week treatment/follow-up period).

2. Schedule of Activities (SoA)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3. Introduction

BOTOX® (Botulinum Toxin Type A) purified neurotoxin complex (United States adopted name onabotulinumtoxinA), administered via intradetrusor injections, is currently approved in more than 80 countries worldwide for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication. A new route of administration, intravesical instillation, is being developed for the treatment of OAB and urinary incontinence.

3.1. Study Rationale

Treatment of OAB and urinary incontinence is highly dependent on the needs and capabilities of the patient. Treatment frequently begins with physiological interventions such as pelvic muscle rehabilitation and fluid and dietary modifications. These programs may be combined with biofeedback and behavioral therapies such as bladder training and toileting assistance. When physiological and behavioral therapies prove insufficient, second line pharmacological agents may be used to reduce the overactivity of the detrusor muscle.

Anticholinergic (antimuscarinic) agents inhibit the binding of acetylcholine to the cholinergic receptors and suppress involuntary detrusor contractions, thereby improving the symptoms of OAB. Treatment with anticholinergics demonstrate a profile of good efficacy but with significant dose-limiting side effects that often result in poor patient adherence/discontinuation as evidenced by repeated cycles of anticholinergic use (Chancellor 2016). Beta-3 adrenergic receptor agonists have a profile of minimal/modest efficacy with cardiovascular side effects and potentially significant drug-drug interaction (Nitti 2013a). After treatment failure with oral or transdermal pharmacologic agents for OAB, the only remaining options currently available are minimally invasive intradetrusor injection of BOTOX which has been recommended by both the American Urological Association (AUA) and the European Association of Urology (EAU) (Gormley 2015; Thuroff 2011), or other more invasive third line recommended procedures such as implantable devices to control incontinence through electrical stimulation of the sacral nerves innervating the bladder or surgical bladder augmentation (Chartier-Kastler 2000; Janknegt 2001; Nitti 2013; Thiagamoorthy 2016).

For patients who are inadequately managed by pharmacologic therapies, or are not suitable candidates for more invasive therapies, there is an unmet medical need for a less invasive, more convenient OAB treatment option. The BOTOX Instillation program will investigate the delivery of BOTOX via intravesical instillation (BOTOX and Hydrogel[1] admixture) in participants with

[redacted]

[redacted]

OAB. Since BOTOX instillation will be administered via a transurethral catheter, this new delivery option will eliminate the need for cystoscopy to administer the treatment. In addition, it will eliminate the need for local anesthesia to the bladder and avoid the use of pretreatment antibiotics which are both required for cystoscopic injections of BOTOX in OAB patients. The results of Study 1839-201-021 will be used to determine the efficacious and safe dose for future investigation in phase 3 clinical trials.

3.2. Background

3.2.1. Overactive Bladder

Overactive bladder (OAB) is a symptom complex that is characterized by the urinary storage symptoms of urgency, with or without urgency incontinence, usually with frequency and nocturia (Abrams 2002). In the normal micturition process, inhibitory messages delivered by the brain to the bladder allow adequate bladder filling and feedback from the bladder to the brain ensures timely voiding. This is accomplished through a complex network of innervation between the detrusor muscle of the bladder and the micturition centers of the brain. When this process is disrupted, patients experience urinary urgency and frequency, which is often associated with urge incontinence, a combination of symptoms referred to generally as OAB. The condition has significant effects on patients' social, psychological, and physical well-being, resulting in depression, reduced quality of life, and poorer sleep quality (Stewart 2003).

Epidemiologic studies in OAB have estimated its worldwide prevalence to be between 50 and 100 million people (Debruyne 2004). In the United States alone, 16.5% of the population (33 million) is estimated to have OAB symptoms, of which approximately 6.1% experience associated urinary incontinence. European studies have similarly reported that approximately 17.0% of the population has symptoms of OAB with approximately 6.0% also associated with urinary incontinence (Milsom 2000). OAB increases with age both in men and women (Stewart 2003). Consequently, it is anticipated that the condition will become more prevalent as the aging population grows larger, thus increasing the already significant economic burden of this disease.

3.2.2. OnabotulinumtoxinA for the Treatment of Overactive Bladder

BOTOX intradetrusor injections have been approved for neurogenic detrusor overactivity (NDO) (BOTOX 200 U) since August 2011 and for OAB (BOTOX 100 U) since January 2013. 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 2010). In addition to its action on the acetylcholine (Ach)-mediated contractions of the detrusor muscle, botulinum toxin serotype A (BoNT/A) may also regulate other vesicle-mediated neurotransmitters in both the afferent and efferent pathways from the bladder wall, urothelium, or lamina propria (Apostolidis 2005; Apostolidis 2006; Collins 2013; Fowler 2002; Franks 2000; Giannantoni 2006; Schulte-Baukloh 2013; Chancellor 2008). Recent data indicate that BOTOX attenuates the bladder afferent nerves involved in

micturition and bladder sensation, suggesting that BOTOX may exert its clinical effects on urinary urgency and the other symptoms of OAB syndrome through its marked effect on afferent nerves at the level of the urothelium (Collins 2013).

3.2.3. Nonclinical Studies

A series of Good Laboratory Practice (GLP) compliant nonclinical pharmacology and toxicology studies with BoNT/A injected into the bladder have been performed. Across all studies BOTOX was well tolerated with no evidence of any serious local or systemic effect, no systemic or local toxicity, and no significant impact on urodynamics.

The systemic toxicity of BOTOX and Hydrogel admixture was evaluated in a 1-month, acute intravesicular instillation toxicity study [redacted] in female rats (20/group) evaluating two instillations [redacted] of BOTOX and Hydrogel admixture at respective BOTOX dose levels of 100, 200, or 400 U/kg at a dose volume of 2 mL/kg. Two additional groups of female rats served as control and received either Hydrogel or saline in the same manner as the treated animals. Procedure-related histological findings including inflammation and/or urothelial hyperplasia in the urinary bladder, ureters, and/or renal pelvis were observed in all groups including the saline control. There were no adverse findings associated with the treatment of the BOTOX and Hydrogel admixture up to 400 U/kg (maximum feasible dose); therefore, the established NOEL in the rats was 400 U/kg.

The local toxicity of BOTOX and Hydrogel admixture was also evaluated in a 1-month, acute intravesicular instillation toxicity study [redacted] in the standard domestic pig (Yorkshire), a model recognized for its similarity to humans in bladder anatomy and volume, with starting weights of around 70 kg. Due to the local nature of the treatment, this allowed for instillation of similar drug doses, volume, and concentrations to that planned for humans, and the ability to use similar drug product instillation processes (ie, techniques and equipment) to that used clinically. In Study [redacted], 30 female domestic Yorkshire pigs underwent a procedure in which a single intravesicular instillation was performed. Nine animals per group were treated with Hydrogel or BOTOX and Hydrogel admixture at a BOTOX dose of 500 U/animal and an additional 12 female animals served as control and received sterile saline in the same manner as the treated animals. The instillation volume was approximately 60 mL in all groups. The animals were maintained for a 2, 14, or 28-day observation period. Intravesicular instillation of saline, Hydrogel or BOTOX and Hydrogel admixture was well tolerated. Microscopic findings in all examined urinary tract tissues from all groups, including saline control, were consistent with spontaneous or incidental background findings in domestic swine or were attributable to minor procedure-associated trauma (hemorrhage in the bladder submucosa), and thus were not considered drug-related.

The BOTOX OAB Instillation Investigator's Brochure provides further detailed information on the non-clinical studies.

3.2.4. Clinical Studies

BOTOX Intradetrusor Injection:

Allergan has completed a clinical development program for intradetrusor injection 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. A brief summary of results is provided below; however, further details can be found in the Investigator's Brochure.

The dose-finding study (Study 191622-077) evaluated a range of BOTOX doses (50 U, 100 U, 150 U, 200 U, and 300 U) versus placebo (N = 313). The phase 3 program 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 of 100 U BOTOX if pre-specified retreatment criteria were fulfilled and 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 150 U BOTOX). 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) (Nitti 2013a; Chapple 2013). In addition, all secondary endpoints were met in both pivotal studies, which included OAB symptoms and other HRQL parameters. The duration of effect of BOTOX, based on the first 100 U BOTOX treatment cycle 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 with a peak effect by Week 2, although majority of the patients did not have an increase greater than 100 mL.

A consistent efficacy and safety profile has been demonstrated with repeat BOTOX treatment with peak efficacy between Week 6 and Week 12 post injection. The reductions from baseline in urinary incontinence episodes remained similar over repeated BOTOX treatments, as did the improvement in HRQL. 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.

BOTOX Intravesical Instillation:

A double-blind, randomized, pilot study with intravesical instillation of BOTOX and Hydrogel in OAB patients has been completed (Krhut 2016). A total of 39 females with OAB symptoms were randomized for the study into 4 groups, receiving 50 mL intravesical instillations [redacted] Key endpoints of the study where the number of urgency grade 3 + 4 episodes/72 h, number of leakage episodes/72 h (both recorded in a 3-day bladder diary), OAB

[redacted]

Questionnaire (OAB-q) total score and Patient Perception of Bladder Condition (PPBC) scale total score both recorded immediately before treatment and 1 month after treatment. Analysis of bladder diary and self-assessment questionnaire data showed superiority of [redacted] 200 U BOTOX over all other groups for number of urgency grade 3< +< 4 episodes/72 h, number of leakage episodes/72 h, Overactive Bladder Questionnaire (OAB-q) total score and PPBC total score. DMSO treatment was superior over all other groups with respect to the number of nocturia episodes/72 h. No serious adverse events were observed during the study. In only one instance (an episode of UTI) was the adverse event considered to be related to the study procedure. No significant effects on the ability to empty the bladder (increase in PVR or decrease in bladder contractility index [BCI]) were recorded. Overall, the results of this pilot study demonstrated that intravesical instillation of BOTOX with Hydrogel was safe and tolerable with efficacy potentially sustained over the course of a few weeks.

3.3. Benefit/Risk Assessment

BOTOX administered via intradetrusor injections is an approved and proven treatment for OAB and urinary incontinence, with a well-established efficacy and safety profile. Intravesical instillation of BOTOX and Hydrogel admixture would offer a less invasive, more convenient OAB treatment option, with the potential to improve the overall patient experience. Although the proposed study will be the first Allergan-sponsored study to evaluate the safety and efficacy of BOTOX and Hydrogel admixture administered via intravesical instillation for the treatment of OAB, the safety profile of BOTOX in humans has been documented in the literature and Allergan clinical study reports in OAB up to doses of 300 U and in a range of indications up to doses of 500 U. Nonclinical Allergan studies evaluating intravesical instillation of BOTOX and Hydrogel admixture in rat and pig models support the safety of the starting dose of BOTOX 100 U in the planned phase 2 study. The established NOEL in rats of 400 U/kg provides an approximately 240- and 48-fold safety margin to the proposed starting dose of 100 U (1.67 U/kg, based on a 60-kg adult human) and maximum dose of 500 U (8.3 U/kg, based on a 60-kg adult human), respectively, in the phase 2 study.

More detailed information about the known and reasonably expected adverse events of BOTOX and Hydrogel admixture administered via intravesical instillation may be found in the investigator's brochure.

4. Objectives and Endpoints

Objectives	Endpoints
• To compare the efficacy of a single treatment of BOTOX intravesical instillation, with possible doses ranging from 100 U to up to 500 U, with placebo in participants with OAB and urinary incontinence	Primary Endpoint: • change from baseline at Week 12 (Stage 2) in the average number of urinary incontinence episodes per day Secondary Endpoint: • change from baseline at Week 12 (Stage 2) in the average number of micturition episodes per day • change from baseline at Week 12 (Stage 2) in the average volume voided per micturition
• To compare the safety of a single treatment of BOTOX intravesical instillation, with possible doses ranging from 100 U to up to 500 U, with placebo in participants with OAB and urinary incontinence	• Adverse events (AEs), physical examination, vital signs, urine dipstick reagent strip test, urinalysis (with urine culture/sensitivity, as applicable), hematology and clinical chemistry, post-void residual (PVR) urine volume, kidney and bladder ultrasound, urine pregnancy test for women of childbearing potential, concomitant medications, concurrent procedures

The efficacy and safety assessments are described in Section 9.

Clinical Hypotheses

BOTOX intravesical instillation (in one or more of the studied doses) is more effective than placebo intravesical instillation at improving the symptoms of OAB as measured by the reduction in urinary incontinence episodes per day, and has an acceptable safety profile.

5. Study Design

5.1. Overall Design

This is a multicenter, randomized, double-blind, placebo-controlled, single-treatment, 2-stage, dose-finding study. The total duration of participant participation in Stage 1 is 14 weeks, including a 2-week screening and 12-week treatment/follow-up period. Total duration of participation in Stage 2 is 28 weeks, including a 4-week screening and 24-week treatment/follow-up period.

For Stage 1, BOTOX intravesical instillation doses (100 U, 300 U, [400 U], 500 U) will be investigated in 3 or 4 consecutive cohorts (Figure 5-1). Upon completion of the Week 6 post instillation follow-up timepoint, safety data from each cohort will be reviewed by an independent data review committee (DRC) prior to starting enrollment into the next dose cohort. Based on the observed safety data from the 100 U and 300 U Cohorts, the DRC will recommend to proceed with either BOTOX 400 U followed by BOTOX 500 U or whether it is safe to dose escalate directly to BOTOX 500 U. Each cohort will be randomized in a 4:1 ratio to receive BOTOX or placebo.

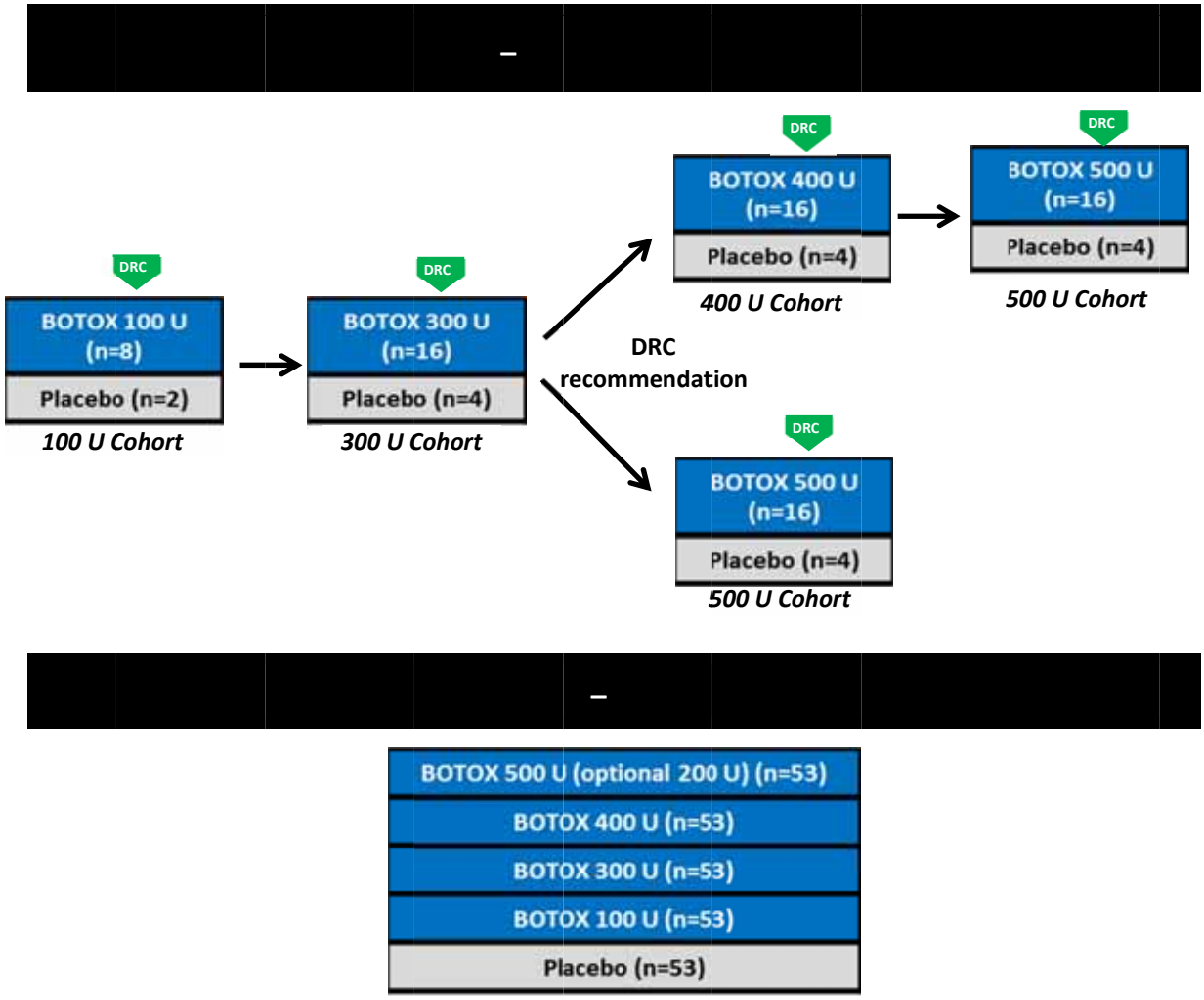
Stage 2 will investigate 4 doses of BOTOX (100 U, 300 U, 400 U, 500 U [or 200 U]) compared to placebo in a 1:1:1:1:1 ratio. Depending on the outcome of DRC review of safety results from the 500 U Cohort in Stage 1, BOTOX 500 U may be replaced with a BOTOX 200 U treatment group (Figure 5-1).

BOTOX or placebo in a Hydrogel admixture will be instilled into the bladder as a single intravesical instillation through a sterile, single use catheter using aseptic technique per local site practice. The total volume to be instilled will be 60 mL.

The primary efficacy measure will be the number of urinary incontinence episodes per day recorded on a 3-day participant bladder diary. Key secondary response measures will be the number of micturition episodes per day and the volume voided per micturition to be recorded on a 3-day participant bladder diary. Additional measures in Stage 2 will include urodynamic parameters [redacted]

[redacted]

Figure 5-1 Schematic of 2-Stage Study Design



[redacted]

5.1.1. Data Review Committee

An independent DRC will review unblinded safety data from Stage 1, upon completion of the Week 6 post-instillation follow-up time point from each cohort. Based on the observed safety data from these reviews, the DRC will recommend to proceed with dose escalation from one cohort to the next. In addition, after review of the safety data in the 100 U and 300 U Cohorts,

the DRC will recommend to proceed with dose escalation either to BOTOX 400 U followed by BOTOX 500 U or whether it is safe to proceed directly to BOTOX 500 U.

The DRC will also recommend to proceed with Stage 2 and select the doses of BOTOX intravesical instillation for further investigation during Stage 2 based on unblinded review of the safety data from the 500 U Cohort in Stage 1.

If additional safety data are required by the DRC prior to proceeding with dose escalation from one cohort (or stage) to the next, additional participants may be enrolled into a cohort as recommended by the DRC.

The DRC will remain in place throughout Stage 2 of the study.

5.2. Participant and Study Completion

Approximately 70 to 100 participants will be screened to randomize ~50 to 70 participants to study treatment in Stage 1. Approximately 380 participants will be screened to randomize ~265 participants to study treatment in Stage 2.

During Stage 1, participants will be enrolled at ~25 sites in the United States. During Stage 2, participants will be enrolled at ~65 sites in North America and Canada.

See Section 10.1 for the rationale for sample size determination.

5.3. End of Study Definition

The end of the study is defined as the date of the last visit or last scheduled procedure shown in the schedule of activities for the last participant in the study.

A participant is considered to have completed the study if he/she is a randomized participant who was treated, has not been discontinued for any reason, attends the scheduled exit visit of the respective stage they were enrolled in, and is properly discharged from the study.

5.4. Scientific Rationale for Study Design

This study is a multicenter, randomized, double-blind, placebo-controlled, single-treatment, 2-stage, dose-finding study. Stage 1 is a placebo-controlled, dose escalation design with 3 or 4 consecutive cohorts and Stage 2 is a 5-arm, placebo-controlled, parallel group design.

Stage 1 is focused on safety, with a dose-escalation design including interim safety assessments and DRC reviews between each dose-escalation cohort. Enrollment into the next cohort at the higher dose will begin only after the DRC has deemed it safe to proceed to the next cohort. The 2-stage study design allows for an assessment of safety during Stage 1 in a conservative, dose-escalating manner prior to the initiation of Stage 2 where the efficacy and safety of BOTOX Instillation will be evaluated in a placebo-controlled, parallel group, 5-arm dose-finding design.

Stage 2 is the dose finding portion of the study, evaluating 4 BOTOX arms and one placebo arm (in a 1:1:1:1:1 design). Randomization will be stratified by baseline urgency urinary incontinence episodes (≤ 9 or > 9 episodes/day) collected during the screening period and by sex to ensure balance across the treatment groups.

Both stages of the study will be randomized and double-blind to minimize investigator and participant bias, and will provide a placebo comparator for evaluating the safety and efficacy of the various BOTOX instillation doses being studied. In addition, relevant safety parameters including adverse events, serious adverse events, physical examination, vital signs, urine dipstick reagent strip test, urinalysis (with urine culture/sensitivity, as applicable), hematology and clinical chemistry, post-void residual urine volume, kidney and bladder ultrasound, urine pregnancy test for women of childbearing potential, concomitant medications and concurrent procedures will be closely monitored throughout the study.

5.5. Justification for Dose

The approved dose for intradetrusor injection of BOTOX in the treatment of OAB is 100 U. Compared with intradetrusor BOTOX injection, the penetration of BOTOX administered via intravesical instillation through the bladder urothelium may be significantly lower due to the indirect method of administration wherein the drug needs to be absorbed through the urothelium rather than being directly injected into the bladder muscle.

The systemic toxicity of BOTOX and Hydrogel admixture was evaluated in a 1-month, nonclinical acute intravesicular instillation toxicity study [redacted] in female rats evaluating two instillations (3 hours apart) of BOTOX and Hydrogel admixture at respective BOTOX dose levels of 100, 200, or 400 U/kg, the NOEL was 400 U/kg (maximum feasible dose). The established NOEL in the rats of 400 U/kg provides an approximately 240- and 48-fold safety margin to the proposed starting dose of 100 U (1.67 U/kg, based on a 60-kg adult human) and maximum dose of 500 U (8.3 U/kg, based on a 60-kg adult human), respectively, in the phase 2 study. The local toxicity of BOTOX and Hydrogel admixture was also evaluated in a 1-month, acute intravesicular instillation toxicity study [redacted] in female domestic Yorkshire pigs. A single intravesicular instillation (volume of ~ 60 mL) of Hydrogel, BOTOX and Hydrogel admixture (at a BOTOX dose of 500 U/animal) or sterile saline, was well tolerated. Microscopic findings in all examined urinary tract tissues from all groups including saline control, were consistent with spontaneous or incidental background findings in domestic swine or were attributable to minor procedure-associated trauma (hemorrhage in the bladder submucosa), and thus were not considered drug-related.

In the planned phase 2 study, the BOTOX and Hydrogel admixture will be introduced in a single cohort of participants at an initial dose of 100 U at a volume of 60 mL. Following the initial cohort, dosing in each subsequent cohort will be based on clinical assessment of the safety data from the previous cohort by an independent DRC.

Overall, results from nonclinical studies evaluating intravesical instillation of BOTOX and Hydrogel admixture in female rats and pigs coupled with the well-established nonclinical safety data and clinical safety profile of BOTOX injection (including cumulative intramuscular injections across indications of up to 500 U as well as previous OAB and NDO development programs with intradetrusor injections up to 300 U), support the initiation of the phase 2 study in OAB participants with a starting dose of 100 U.

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The population consists of participants with OAB and urgency urinary incontinence who have an inadequate response to or are intolerant of pharmacologic therapy.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1.	**Age**
1.01	Must be 18 to 75 years old at the time of signing the informed consent.
2.	**Type of Participant and Disease Characteristics**
2.01	Has symptoms of OAB (frequency and urgency) with urgency urinary incontinence for a period of at least 6 months immediately prior to screening, determined by documented participant history.

2.04	Has not been adequately managed with ≥ 1 pharmacologic therapies for treatment of their OAB symptoms (ie, anticholinergics or beta-3 agonists), in the opinion of the investigator. [redacted]
[redacted]	
4.	**Sex**
4.01	Male or female participant
5.	**Contraceptives**
5.01	Has a negative pregnancy test result (for women of childbearing potential).
6.	**Informed Consent**
6.01	Written informed consent from the participant has been obtained prior to any study-related procedures.
6.02	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 (EU sites).
[redacted]	

[redacted]

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1.	**Medical Conditions**
1.01	Has symptoms of OAB due to any known neurological condition (eg, spinal cord injury, multiple sclerosis, cerebrovascular accident, Alzheimer's disease, Parkinson's disease, etc).
1.02	Has a predominance of stress incontinence in the opinion of the investigator, as determined by participant medical history
1.03	Has history or evidence of any pelvic or urological abnormalities [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.03	Has had previous or current botulinum toxin therapy of any serotype for any urological condition.

[redacted]

[redacted]

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

There are no specific requirements regarding diet. [redacted]

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

7. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Study Treatment Name	BOTOX and Hydrogel Admixture	BOTOX Placebo and Hydrogel Admixture
Dosage Formulation	BOTOX [redacted] *Clostridium botulinum* toxin Type A in a sterile vacuum-dried form to be reconstituted with 0.9% sterile saline (without preservative) Hydrogel (RTGel™) [redacted] Each vial of Hydrogel contains [redacted] BOTOX and Hydrogel Admixture[b]: Reconstituted BOTOX to be administered with Hydrogel for intravesical instillation	BOTOX Placebo [redacted]: each vial contains 0.9 mg of sodium chloride in a sterile, vacuum-dried form to be reconstituted with 0.9% sterile saline (without preservative) Hydrogel (RTGel™) [redacted]: Each vial of Hydrogel contains [redacted] BOTOX Placebo and Hydrogel Admixture[b]: Reconstituted BOTOX Placebo to be administered with Hydrogel for intravesical instillation
Route of Administration	Intravesical instillation	Intravesical instillation
Dosing Instructions	Single treatment (60 mL volume) administered by the investigators or study site personnel qualified to place a transurethral catheter.	Single treatment (60 mL volume) administered by the investigators or study site personnel qualified to place a transurethral catheter
Packaging and Labeling	BOTOX will be provided in vials in identical packaging and labeling to placebo. [redacted]	BOTOX Placebo will be provided in vials in identical packaging and labeling to BOTOX. [redacted]
Manufacturer	BOTOX: Allergan Inc. Hydrogel (RTGel™): [redacted]	BOTOX Placebo: Allergan Inc. Hydrogel (RTGel™): [redacted]

[redacted]

[redacted]

7.1.1. Treatment Regimen and Dosing

All eligible participants enrolled into the study will receive a single double-blind treatment of either BOTOX or placebo for Stage 1 or Stage 2 as follows:

Stage 1

- 100 U Cohort: 100 U BOTOX intravesical instillation (BOTOX and Hydrogel admixture) (n = 8) or placebo (n = 2)
- 300 U Cohort: 300 U BOTOX intravesical instillation (BOTOX and Hydrogel admixture) (n = 16) or placebo (n = 4)
- 400 U Cohort (optional): 400 U BOTOX intravesical instillation (BOTOX and Hydrogel admixture) (n = 16) or placebo (n = 4)
- 500 U Cohort: 500 U BOTOX intravesical instillation (BOTOX and Hydrogel admixture) (n = 16) or placebo (n = 4)

Based on the observed safety data from the 100 U and 300 U Cohorts, the DRC will recommend to proceed with either BOTOX 400 U followed by BOTOX 500 U or whether it is safe to dose escalate directly to BOTOX 500 U.

Stage 2

- 100 U BOTOX intravesical instillation (BOTOX and Hydrogel admixture) (n = 53)
- 300 U BOTOX intravesical instillation (BOTOX and Hydrogel admixture) (n = 53)
- 400 U BOTOX intravesical instillation (BOTOX and Hydrogel admixture) (n = 53)
- 500 U (option to replace with 200 U) BOTOX intravesical instillation (BOTOX and Hydrogel admixture) (n = 53)
- BOTOX Placebo intravesical instillation (Placebo and Hydrogel admixture) (n = 53)

The four BOTOX doses for investigation in Stage 2 will be selected based on the review of unblinded safety data from the 500 U Cohort in Stage 1 by the DRC. The DRC will have the option to replace the 500 U treatment group with BOTOX 200 U in Stage 2.

7.1.2. Day of Treatment Criteria

The following day of treatment criteria must be fulfilled prior to administration of study treatment at randomization/Day 1:

- Central laboratory urine analysis results for possible UTI have been reviewed

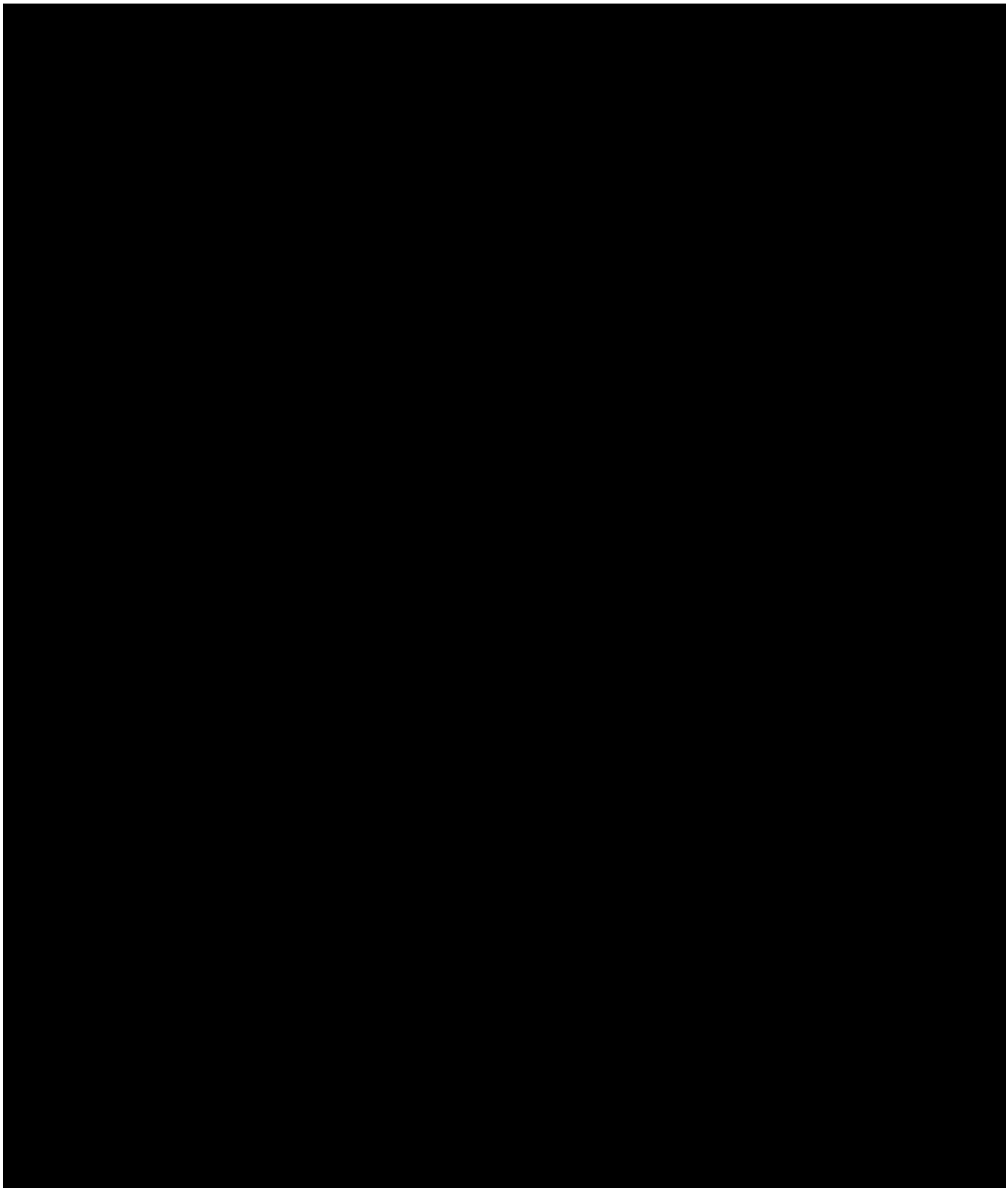
- Negative urine dipstick reagent strip test (for nitrates and leukocyte esterase) performed at the study site
- Participant is asymptomatic for a UTI, in the opinion of the investigator
- Negative urine pregnancy test for women of childbearing potential
- Investigator continues to deem that no condition or situation exists which, in the investigator's opinion, puts the participant at significant risk from receiving an intravesical instillation of BOTOX

7.1.3. Instillation Procedure

Treatment administration must be performed by the investigator, subinvestigator(s) or study site personnel qualified to place a transurethral catheter.

In order to provide guidance to qualified site personnel who have been delegated the role of study treatment administrator, the investigator is expected to perform or be present for at least the first instillation procedure performed at the site.

[redacted]



[redacted]

7.2. Dose Modification

Not applicable.

7.3. Method of Treatment Assignment

Prior to initiation of study treatment, each participant who provides informed consent will be assigned a participant number that will serve as the participant identification number on all study documents.

For Stage 1, participants will be randomized centrally on randomization/Day 1 using an automated randomization system to 1 of 2 treatment groups within each cohort in a 4:1 ratio to receive BOTOX and Hydrogel admixture or placebo and Hydrogel admixture.

For Stage 2, participants will be randomized and stratified centrally on randomization/Day 1 by baseline urgency urinary incontinence episodes (≤ 9 or > 9 episodes/day) and sex collected during the screening period. Each participant within a stratification group will be randomized using an automated randomization system to 1 of 5 treatment arms (BOTOX 100 U and Hydrogel admixture, BOTOX 300 U and Hydrogel admixture, BOTOX 400 U and Hydrogel admixture, BOTOX 500 U [or BOTOX 200 U] and Hydrogel admixture, placebo and Hydrogel admixture) in a ratio of 1:1:1:1:1.

[redacted]

7.4. Blinding/Masking

All investigational study treatments (BOTOX and placebo) will have identical packaging and labeling to maintain masking of the study. Study treatments will be identified as investigational compounds. [redacted]

The Hydrogel will not be masked and will be provided to sites in an open-label fashion. Hydrogel for intravesical instillation with BOTOX/BOTOX Placebo will be identified as an investigational compound. [redacted]

When necessary for the safety and proper treatment of the patient, the investigator can unmask the participant's treatment assignment to determine which treatment 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.

[redacted]

7.5. Preparation/Handling/Storage/Accountability

Detailed reconstitution instructions will be included in the Study Pharmacy Manual.

The study medication must be stored in a secure area and administered only to participants entered into the clinical study, at no cost to the participant, in accordance with the conditions specified in this protocol. Only authorized site staff may supply or administer study treatment.

[redacted]

[redacted]

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

[redacted]

7.6. Treatment Compliance

Study treatment will be administered by the investigator or study site personnel qualified to place a transurethral catheter.

7.7. Concomitant Therapy

The use of any concomitant medication, prescription or over-the-counter, is to be recorded on the participant's electronic case report form (eCRF) at each visit along with the reason the medication is taken.

7.7.1. Prohibited Treatments and Washout Before the Study

Prohibited medication washout of pharmacologic therapy to treat symptoms of OAB, including nocturia, must be complete prior to the first screening procedure. [redacted]

7.7.2. Permitted Treatments

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/treatment is in question, please contact the sponsor.

The sponsor or designee should be contacted if there are any questions regarding concomitant or prior therapy.

Caution is advised if the participant requires treatment with aminoglycoside antibiotics or curare-like agents during the course of the study. This is due to the potential interaction of these

treatments with BOTOX, which may affect the neuromuscular junction and may therefore result in an unpredictable effect on muscle weakness.

7.7.3. Prohibited Treatments During the Study

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.

Prior botulinum toxin treatment of any serotype for any urological condition is prohibited.

[redacted]

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation/Withdrawal Criteria

Participants may voluntarily withdraw from the study at any time.

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRF. If a participant exits the study prior to study completion, all exit visit assessments should be performed at the time of exit.

8.1. Discontinuation of Study Treatment

See the schedule of activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

Reasons for discontinuation from the study treatment and/or the study may include the following:

- Adverse event
- Completed
- Death
- Failure to meet randomization criteria
- Lack of efficacy
- Lost to follow-up
- Other
- Pregnancy
- Protocol deviation
- Site terminated by sponsor
- Study terminated by sponsor
- Technical problems
- Withdrawal by participant

These terms are defined in Appendix 5.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

- Participants must be discontinued from the study and/or receive no further study treatment, if any of the following criteria are met:

    - Participant develops (or has an exacerbation of) any medical condition or adverse event that, in the opinion of the investigator, would put the participant at an unacceptable medical risk or compromises the participant's ability to participate in the study

    - Participant becomes pregnant (see Section 9.2.5)

    - Participant is diagnosed with new or recurrent malignancy, except basal cell carcinoma

    - Participant is unwilling or unable to continue to comply with study procedures

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

- Participants should be followed for at least 12 weeks post study treatment. All participants who prematurely discontinue from the study, unless the cause is screen failure, should be seen for a final assessment at early termination. A final assessment will be defined as completion of the evaluations scheduled for the final visit at Week 12/Exit for Stage 1 or Week 24/Exit for Stage 2.

- The investigator and Allergan also have the right to withdraw a participant from the study at any time for any reason.

- Where possible, the decision to withdraw a participant from study treatment or the study should be discussed with Allergan.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

[redacted]

9. Study Assessments and Procedures

- Study procedures and their timing are summarized in the schedule of activities (Section 2).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Screening procedures can commence once the informed consent and data authorization/protection form have been obtained. Screening will be considered to have started at the time of the first screening activity or procedure, and completed when all the required inclusion/exclusion criteria have been met and the patient is randomized at Day 1.

Screening procedures should be completed as soon as possible, with a maximum of -14 day window from randomization/Day 1 for Stage 1 and maximum of -28 day window from randomization/Day 1 for Stage 2. The patient will be considered enrolled into the study upon randomization at Day 1. If the patient has a positive urine dipstick test result and needs to be treated for a UTI, the screening period can be extended by up to 14 days. Screening procedures may be repeated during this time, as deemed clinically necessary, at the discretion of the investigator (eg, repeat the 3-day bladder diary if patient had a symptomatic UTI during initial diary collection).

- Evaluations should be performed by the same evaluator throughout the study whenever possible.

9.1. Efficacy Assessments

Only Stage 2 is powered for an inferential efficacy analysis.

9.1.1. Primary Efficacy Measure

Number of episodes of urinary incontinence per day, as recorded in the participant bladder diary over 3 consecutive days during the week prior to each study visit. The primary timepoint is at Week 12.

9.1.2. Secondary Efficacy Measures

- Number of episodes of micturition per day (both by voluntary urination and by catheterization, if required) as recorded in the participant bladder diary over 3 consecutive days during the week prior to each study visit.

- Volume voided per micturition as recorded over one 24-hour period during the 3-day bladder diary (divided by the number of micturitions in the same 24-hour period).

[redacted]

[redacted]

[redacted]

[redacted]

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study (see Section 8).

9.2.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs from the signing of the ICF until 30 days after the last follow-up visit will be collected at the timepoints specified in the schedule of activities (Section 2), and as observed or reported spontaneously by study participants.

All AEs from the signing of the ICF until the last follow-up visit will be collected at the timepoints specified in the schedule of activities (Section 2), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the AE section of the eCRF.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. Pregnancy

Urine pregnancy testing will be conducted for women of childbearing potential at screening, Day 1 (prior to treatment), and at each follow-up clinic visit. See Appendix 4 for detailed information on definition of women of childbearing potential, use of contraceptives and pregnancy.

If a female becomes pregnant during the study, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4. The participant will be exited from the study after appropriate safety follow-up.

Details of all pregnancies in female participants will be collected after the start of study treatment. The investigator will (1) notify the participant's physician that the participant was being treated with the investigational drug, 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. Please see Appendix 4 for further information on collection of pregnancy information

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.2.6. 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 participant has an elevated PVR that requires intervention with CIC according to the following criteria:

- Participant has a PVR of ≥ 350 mL (regardless of symptoms), OR
- Participant has a PVR ≥ 200 mL and < 350 mL and the participant reports associated symptoms ie, voiding difficulties, sensation of bladder fullness 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.

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

Definition of Adverse Event of Urinary Tract Infection

An adverse event of UTI will be recorded if all of the following criteria are fulfilled:

- Participant has symptoms of a UTI (eg, painful urination, fever, hematuria, etc)
- A positive urine culture result with a bacteriuria count of > 10^5 CFU/mL
- Leukocyturia of > 5/hpf.

If a patient has symptomatic leucocyturia and/or symptomatic bacteriuria but does not meet the above criteria for a UTI, "symptomatic leucocyturia" and/or "symptomatic bacteriuria" are recorded individually as adverse events and the symptoms (e.g. dysuria) are reported separately as well.

If a participant reports a UTI to the investigator which 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.

If a participant is asymptomatic, but has:

- a clinically significant bacteriuria (with or without leucocyturia), this should be reported as "asymptomatic bacteriuria".
- a clinically significant leucocyturia, (with or without bacteriuria), this should be reported as "leucocyturia"

9.3. Treatment of Overdose

The LD_{50} for BOTOX in humans is estimated from primate studies to be approximately 3000 U. This makes accidental injection of a lethal dose highly unlikely, but significant AEs may still occur at doses below the LD_{50} (Herrero 1967; Scott 1989). Excessive doses may produce local, or distant, generalized, and profound neuromuscular paralysis. Should accidental injection or oral ingestion occur or overdose be suspected, the patient should be medically monitored for up to several weeks for progressive signs or symptoms of systemic muscular weakness that could be local or distant from the site of injection, which may include ptosis, diplopia, dysphagia, dysarthria, generalized weakness, or respiratory failure. Please refer to the BOTOX (OAB Instillation) Investigator's Brochure (General Section; Section 6.5 Overdose) for further details.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for AEs/SAEs and laboratory abnormalities.
3. Document the quantity of the excess dose, as well as other details that led to overdose, in the eCRF.

9.4. Safety Assessments

Planned timepoints for all safety assessments are provided in the schedule of activities (Section 2).

9.4.1. Physical Examinations

The physician or appropriately qualified designee will perform a complete physical examination and examine the participant for any physical abnormalities of the following body systems: head, ears, eyes, nose, and throat (HEENT), neck, heart/cardiovascular, pulmonary, abdomen, musculoskeletal, skin, and genitourinary (full pelvic and rectal examination for females and rectal examination for males). Physical examination will be performed at the appropriate scheduled visits (Table 2-1 and Table 2-2).

9.4.2. Vital Signs

Vital signs will be measured as outlined below:

- pulse rate (beats per minute): participants should be resting in a seated position
- blood pressure (mm Hg): participants should be resting in a seated position. Systolic/diastolic blood pressure is then measured with a sphygmomanometer
- temperature (^{o}F or ^{o}C): participants should be seated and the body temperature taken according to local site practice
- body weight (screening and exit visits) and height (Screening visit only) will be measured according to local site practice

Please see the schedule of study visits (Table 2-1 and Table 2-2) for the visits at which vital signs should be assessed.

9.4.3. Clinical Safety Laboratory Assessments

All clinical laboratory samples will be analyzed [redacted]

Analytes will be tested as specified below:

Hematology: red blood cells (RBC); white blood cells (WBC); WBC differential (% and absolute): neutrophils, lymphocytes, monocytes, eosinophils, basophils, hematocrit, hemoglobin, platelets

Blood Chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT [SGPT]), aspartate aminotransferase (AST [SGOT]), total and direct bilirubin, blood urea nitrogen (BUN), calcium, chloride, creatinine, gamma glutamyltransferase (GGT), globulin, nonfasting glucose, potassium, total protein, and sodium

Urinalysis and Urine Culture and Sensitivity: Urinalysis will be performed at all clinic study visits as applicable; a urine culture and sensitivity test will also be performed as determined by the central laboratory when urinalysis results are suggestive of a UTI (positive leukocyte esterase, nitrites, blood and/or microscopic sediments such as WBCs, RBCs, and/or bacteria). Urine analytes to be tested are listed below:

- Urinalysis: color, appearance, specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin, urobilinogen, crystals; microscopic examination if positive for protein, leukocyte, occult blood, nitrite, or crystals

- Urine Culture and Sensitivity: culture, quantitation, isolation, identification, and susceptibility

Urine Dipstick Reagent Test (Urine Dipstick) Test: The urine dipstick is used to identify a potential UTI and to provide immediate information to the investigator. If positive for nitrites and/or leukocyte esterase, indicating a possible infection, the participant should be treated with antibiotics per the clinical judgment of the investigator and in accordance with local site practice. Urine analysis, urine culture and sensitivity testing (performed from a sample collected on the same day as the dipstick) will be used to confirm the presence or absence of a UTI. If UTI is present, sensitivity testing will provide additional information to the investigator regarding pathogen susceptibility to the antibiotic selected for treatment based on the positive dipstick.

- Screening urine dipstick reagent strip test results: If positive, the screening period can be extended by up to 14 days (ie, a total maximum of 28 days for Stage 1 and 42 days for Stage 2) to accommodate the additional time required for antibiotic treatment. Some of the screening procedures may be repeated, as deemed clinically necessary, at the discretion of the investigator (eg, repeat the screening bladder diary if participant had a symptomatic UTI during initial diary collection).

- Randomization/Day 1 urine dipstick reagent strip test results: Participants with a dipstick positive for nitrites and/or leukocyte esterase at randomization/Day 1 do not meet "day of treatment criteria" and therefore must not receive study treatment. The participant should be treated with antibiotics per the clinical judgment of the investigator and in accordance with local site practice and may return for a rescheduled randomization/Day 1 visit (within a total maximum of 28 days of starting screening procedures for Stage 1 and a total maximum of 42 days of starting screening procedures for Stage 2). If the dipstick obtained at the rescheduled randomization/Day 1 visit is negative for nitrites and leukocyte esterase and all "day of treatment criteria" are fulfilled, the participant can be treated.

Urine cytology: Urine cytology is performed at the screening visit only. Abnormal urine cytology suspicious for a urothelial malignancy should be investigated by the investigator according to local site practice, and only if such malignancy is ruled out should the participant be enrolled. Results of the investigation will be recorded in the source documents.

Prostate-specific Antigen (PSA): PSA levels will be measured at screening in male participants.

Urine Pregnancy Test: Urine pregnancy testing will be conducted for women of childbearing potential.

9.4.4. Post-void Residual Urine Volume

PVR urine volume is assessed by ultrasound or bladder scan after the participant has performed a voluntary void. If a participant is required to begin use of CIC post treatment, the PVR urine volume will be measured after the participant has attempted to void voluntarily and prior to a catheterization. If a participant is not able to spontaneously void despite trying, then this will be recorded on the CRF and the PVR will not be measured.

After randomization, should a PVR urine volume indicate a clinically meaningful elevation, the participant should be asked to void once again (allowing the participant sufficient time to void). The PVR urine volume will then be re-assessed. For participants 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 additional follow-up 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 participant. The need for CIC is also dependent on the PVR as well as the participant symptoms. This guidance is to ensure participants 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. Participant continues to be followed 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 participant 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 participant 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 (Section 9.4.5).

b) If a participant 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 participant 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 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 participant 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 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 additional follow-up visits should occur
    - If the PVR is decreasing or is unchanged then the participant will continue per the protocol 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.

9.4.5. Clean Intermittent Catheterization

The following guidance should be used for the initiation of CIC in this study. Sterile, single use intermittent catheters should be used. Indwelling catheters should not be used in this study.

Initiation of Clean Intermittent Catheterization

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

- PVR is ≥ 350 mL at any posttreatment visit, regardless of whether the participant reports associated symptoms
- PVR is ≥ 200 mL and < 350 mL and the participant 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 (for elevated PVR as described above):

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

Once CIC is initiated, the status of CIC use should be documented in the participant record at each visit (ie, use/nonuse).

Cessation of Clean Intermittent Catheterization

CIC should be discontinued when the following criteria are fulfilled:

- the participant does not have any associated symptoms which in the opinion of the investigator require CIC AND
- the PVR is < 350 mL

The date of discontinuation of CIC should be documented. If the investigator deems that CIC should not be discontinued even though the above criteria are fulfilled, then this should be documented and the reason given. Upon discontinuing CIC the participant will be seen for a follow-up visit 1 week later where the PVR, associated symptoms, central laboratory urine

analysis and culture/sensitivity will be reassessed. The investigator will determine whether the participant can then be followed at regularly scheduled study visits or whether additional follow-up visits should occur based on PVR and/or associated symptoms.

9.4.6. Bladder and Kidney Ultrasound

Abdominal ultrasound of the bladder and kidneys will be performed with the bladder at least half full. Participants are excluded from this study if the screening ultrasound demonstrates the presence of bladder stones and/or intra-luminal filling defects of the bladder suggestive of malignancy. In the case of unclear new findings identified at the exit visit ultrasound which may be suggestive of stones (kidney, ureter, or bladder), other diagnostic measures must be performed in order to confirm the presence of stones, rule out bladder malignancy (eg, x-ray with or without contrast, urogram, CT scan, MRI or cystoscopy and histopathological confirmation).

9.4.7. Concomitant Medications and Concurrent Procedures

Concurrent procedures and concomitant medication (including name of medication, dose, route, and date) information will be collected at each study clinic and phone visit starting at the time of screening and ending at the participant Exit Visit. All concomitant medications and concurrent procedures must be recorded in the eCRF with all specific details associated with each use of the medication/procedure.

9.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

[redacted]

10. Statistical Considerations

10.1. Sample Size Determination

For Stage 1, approximately 50 to70 participants will be enrolled to ensure that 10 to 20 individuals are randomized into each of the 4 cohorts (100 U Cohort: n = 10; 300 U Cohort: n = 20; 400 U Cohort: n = 20; 500 U Cohort: n = 20) to provide sufficient data in the analysis and interpretation of safety results. Two particular adverse events of interest are urinary retention and UTI. From previous BOTOX studies, the percentage of participant in the BOTOX-treated population experiencing these adverse events is 6% to 7% for urinary retention and 20% to 30% for UTI. In cohort 1, the probability of observing at least one BOTOX-treated participant experiencing these adverse events is 0.39 to 0.44 and 0.83 to 0.94, respectively. For the other cohorts, the probability of observing at least one BOTOX-treated participant experiencing these adverse events is 0.63 to 0.69 and 0.97 to ~ 1, respectively.

For Stage 2, 50 participants are required for each of the 4 BOTOX treatment groups and 50 participants are required for the placebo group in order to obtain approximately 72% power to detect a between group difference of 1.8 episodes in change from baseline to Week 12 in the number of episodes of urinary incontinence per day between the BOTOX and placebo treatment groups. Sample size calculations are based on a two-sample t-test assuming a common standard deviation (SD) of 3.5 episodes and a 2-sided type I error rate of 0.05. In order to account for participant attrition (estimated to be 5%), the sample size was increased to 53 participants for each treatment group, amounting to a total of 265 randomized participants required for Stage 2. Additionally, using these samples sizes, the probability of observing at least one occurrence of urinary retention or UTI in the BOTOX-treated population in Stage 2 is nearly 1.

Table 10-1 Sample Size Assumptions for Stage 2

Parameter	Assumption/Estimate
Primary endpoint	Change from baseline to Week 12 in the number of episodes of urinary incontinence per day between BOTOX and placebo treatment groups
Mean/risk difference[a]	1.8 episodes
SD[a]	3.5 episodes
α	0.05
Sides	2
Power	72%
N per group	50
Attrition rate	5% at Week 12
N total	265
N per group estimated	53

[a] Based on previous BOTOX studies and relevant details

Overall, a total of 315 to 335 randomized participants are required for the entire study.

10.2. Populations for Analyses

The analysis populations will consist of participants as defined below:

Table 10-2 Analysis Populations

Population	Definition	Study Treatment
Screened	All screened participants who sign informed consent	—
Enrolled	All the participants who sign informed consent and screened with eligibility verified	—
Intent-to-treat (ITT)	For Stages 1 and 2, the ITT populations will include all randomized participants. The efficacy data will be analyzed as randomized using the ITT populations for Stages 1 and 2 separately. The primary efficacy analysis will be performed in Stage 2 on the ITT population when all study participants reach Week 12.	Randomized treatment assignment
Safety	For Stages 1 and 2, the safety population will include all participants enrolled in this study who received the study treatment.	Actual treatment received

10.3. Statistical Analyses

The 2-stage study design described in Section 5.1 was selected to satisfy two separate goals in a specific sequence. The focus of Stage 1 of the study is establishing safety whereas Stage 2 is intended to identify the most efficacious dose. For Stage 1, the analyses of safety endpoints will take primacy; analysis of efficacy endpoints will be supplemental. For the prior reason, efficacy analyses for Stage 1 will be descriptive in nature only; no inferential testing will be performed.

The statistical analysis plan (SAP) will be developed and finalized before database lock for stages 1 and 2, separately. SAP will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

This section is a summary of the planned statistical analyses of the primary and secondary endpoints for Stage 2

10.3.1. Key Statistical Methodology

The methodologies defined below apply as specified to individual endpoints.

Table 10-3 Statistical Methodology

Methodology	Description
Categorical counts	• Number of participants in individual categories o Participants with ≥ 1 qualifying event counted once per individual category
Categorical descriptives	• Number and percentage of participants in individual categories o Participants with ≥ 1 qualifying event counted once per individual category • N1 if percentage denominator ≠ number of participants in the population (standard

Methodology	Description
	percentage denominator) o N1 = participants with nonmissing baseline value
PCS descriptives	• Number and percentage of participants meeting potentially clinically significant (PCS) criteria o Participants with ≥ 1 qualifying event counted once per PCS category • Percentage denominator = number of participants with nonmissing baseline and ≥ 1 nonmissing postbaseline assessment o Unevaluable assessments considered missing
Event descriptives	• Number and percentage of events in individual categories o Events counted individually for each instance • Percentage denominator = total number of events
Shift analysis	• Number and percentage of participants in individual baseline and postbaseline categories • Percentage denominator = number of participants in individual baseline categories • N1 = participants with nonmissing values at both baseline and the specified postbaseline analysis visit
Continuous descriptives	• N1, mean, SD, median, minimum, maximum • N1 = participants with nonmissing value
CFB descriptives	• Continuous descriptives for baseline, postbaseline, and change from baseline (CFB) values • N1 = participants with nonmissing values at baseline visit • Missing values replaced by the last observation carried forward (LOCF)
CFB ANCOVA	• Continuous descriptives and standard error (SE) for baseline, postbaseline, with LOCF,and CFB values • Estimates derived from mixed model for CFB value controlling for factors (treatment group and stratification variables) and covariates (baseline value) o Least squares (LS) means and standard errors o LS mean differences, standard errors, and 95% confidence intervals vs placebo o P-values from contrast t-test comparing [BOTOX dose groups vs placebo] • N1 = participants with nonmissing values at baseline
CFB ANCOVA Sensitivity	• Continuous descriptives and standard error (SE) for baseline, postbaseline with only observed values, and CFB values • Estimates derived from mixed model for CFB value controlling for factors (treatment group and stratification variables) and covariates (baseline value) o Least squares (LS) means and standard errors o LS mean differences, standard errors, and 95% confidence intervals vs placebo • P-values from contrast t-test comparing [BOTOX dose groups vs placebo] • N1 = participants with nonmissing values at both baseline and the specified postbaseline analysis visit

Methodology	Description
Responder	• Categorical descriptives for responders and nonresponders o Nonresponders include: ▪ Participants who do not meet responder criteria ▪ Participants with no postbaseline values • 95% confidence interval for the proportion • Estimates derived from Cochran-Mantel-Haenszel (CMH) model controlling for stratification factors o Mantel-Haenszel (MH) odds ratios (ORs) and confidence intervals vs placebo o P-values for the adjusted odds ratio of BOTOX dose groups vs placebo • N1 = all participants unless otherwise specified
Time-to-event	• Categorical descriptives for participants with events and censoring o Censoring includes: ▪ Participants who do not meet event criteria ▪ Participants with no postbaseline values • Quartiles and 95% confidence intervals for median derived from Kaplan-Meier (KM) nonparametric model using log-log transformation of survival function • Estimates derived from log-rank model controlling for stratification factors o P-values comparing BOTOX dose groups vs placebo • N1 = all participants unless otherwise specified
KM figure	• Step-function figure of [survival function/cumulative distribution function [1 – survival function]] estimates with censoring indicators, derived from KM nonparametric model

ANCOVA = analysis of covariance; ANOVA = analysis of variance; CFB = change from baseline; Cochran-Mantel-Haenszel; KM = Kaplan-Meier; LOCF = the last observation carried forward; TTE = time-to-event.

10.3.1.1. Hypothesis

For the primary efficacy analysis, the null hypothesis is that there is no difference between each BOTOX and Hydrogel admixture group and placebo and Hydrogel admixture group as measured by the change from baseline in daily average number of urinary incontinence episodes at Week 12 post-study treatment. The alternative hypothesis is that there is a difference between each BOTOX and Hydrogel admixture group and placebo and Hydrogel admixture group as measured by change from baseline in daily average number of urinary incontinence episodes at Week 12.

10.3.1.2. Methods of Analysis

In general, baseline is defined as the last nonmissing assessment before Day 1. Continuous variables will be summarized with descriptive statistics (sample size, mean, median, standard deviation, minimum, and maximum values). Categorical variables will be summarized with frequency distributions (counts and percentages).

10.3.2. Efficacy Analyses

10.3.2.1. Collection and Derivation of Primary and Secondary Efficacy Measures

Primary Measure (Number of urinary incontinence episodes [UIE] per day):

UIE will be recorded in a 3-day bladder diary and calculated as the average number of episodes per day over a consecutive 3-day period.

The participant's baseline number of UIE will be the average from the 3 reported consecutive days immediately prior to randomization.

Secondary Measures (Number of micturition episodes per day and Volume voided per micturition):

Both secondary measures will be recorded by the participant on the same diary. Number of micturition episodes per day will be calculated based on a consecutive 3-day average. The volume voided per micturition will be calculated from the total urine volume from micturitions (toilet voids or catheterizations) over one 24-hour period during the 3-day participant bladder diary divided by the number of micturitions in the same 24-hour period.

Missing Data

Every effort will be made to obtain required data at each scheduled evaluation from all participants who have been enrolled. The last observation carried forward (LOCF) imputation method will be used for the primary analysis in Stage 2. Sensitivity analyses will be performed using only observed data.

10.3.2.2. Primary and Secondary Efficacy Analyses

Primary Efficacy Variable

The primary efficacy variable is the change in the average number of urinary incontinence (UIE) episodes per day from baseline. The primary timepoint will be Week 12 after instillation.

The primary variable will be calculated based on change from baseline of the consecutive 3-day average at each scheduled study visit. Calculation of averages will employ available data without imputation. If no data are available for the consecutive 3-day period, that average will be considered missing for that participant.

Secondary Efficacy Variables

The secondary efficacy variables are the change from baseline for the average number of micturition episodes per day and average volume voided per micturition. The primary timepoint will be Week 12 after instillation in Stage 2.

The secondary variables will be calculated based on change from baseline of the consecutive 3-day average at each scheduled study visit. Calculation of averages will employ available data without imputation. If no data are available for the consecutive 3-day period, that average will be considered missing for that participant.

Endpoint	Description	Timing	Methodology
Endpoint 1	change in the average number of UIE at Week 12 from baseline with LOCF	Weeks 1 – 24	CFB descriptives CFB ANCOVA
Endpoint 2	change in the average number of UIE at Week 12 from baseline with observed values	Weeks 1- 24	CFB descriptives CFB ANCOVA Sensitivity
Endpoint 3	change from baseline in the average number of micturition episodes per day to Week 12	Weeks 1 – 24	CFB descriptives CFB ANCOVA
Endpoint 4	change from baseline in volume voided per micturition to Week 12	Weeks 1 – 24	CFB descriptives CFB ANCOVA

ANCOVA = analysis of covariance; CFB = change from baseline; LOCF = the last observation carried forward; UIE = urinary incontinence episodes.

10.3.2.3. Multiple Comparisons Procedure

There will be no adjustments for multiple comparisons.

[redacted]

[redacted]

10.3.4. Safety Analyses

The following safety categories will be summarized as appropriate (eg, categorical or continuous descriptives, shift tables) for the safety population and will be fully defined in the SAPs.

- Adverse events

- Physical examination
- Vital signs (pulse rate, blood pressure, and body temperature)
- Urine dipstick reagent strip test
- Urinalysis (with urine culture/sensitivity, as applicable)
- Hematology and clinical chemistry
- PVR urine volume
- Kidney and bladder ultrasound
- Urine pregnancy test for women of childbearing potential
- Concomitant medications
- Concurrent procedures

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ classification (SOC) using MedDRA. For each adverse event reported, the number and percent of participants will be tabulated based on the preferred term. The tables will be generated by relationship to treatment as well as by system organ class and severity.

[redacted]

10.3.6. Analyses Timepoints and Scope

There will be a database lock for Stage 1 and 2 database locks for Stage 2: one for primary and one for final. Stage 1 and Stage 2 will be analyzed separately. In addition, safety data for the first 12 weeks from each stage will be pooled. At the end of Stage 1, selected safety and efficacy analyses may be performed.

Primary and final analyses are planned for Stage 2. In Stage 2, the primary analysis will be conducted when all randomized participants have completed at least 12 weeks of follow-up post-randomization (or prematurely exited the study prior to Week 12). The final analysis will be performed on study completion. Details of the primary analyses and final analysis will be described in separate SAPs.

The statistical analysis plans will describe the analyses in greater detail.

[redacted]

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12. Appendices

12.1. Appendix 1: Abbreviations and Trademarks

Term/Abbreviation	Definition
AE	adverse event
ANCOVA	analysis of covariance
AUA	American Urological Association
BCI	bladder contractility index
BoNT/A	botulinum toxin serotype A
BOTOX	Botulinum Toxin Type A Purified Neurotoxin Complex (US Adopted Name is onabotulinumtoxinA)
CFB	change from baseline
CMH	Cochran-Mantel-Haenszel
CIC	clean intermittent catheterization
DMSO	dimethyl sulfoxide
DRC	data review committee
eCRF	electronic case report form
EAU	European Association of Urology
EDC	electronic data capture
FSV	first sensation to void
GCP	Good Clinical Practices
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act
HRQL	health-related quality of life
Hydrogel	Hydrogel refers to RTGel™ [redacted]
ICH	International Conference on Harmonisation
IDC	involuntary detrusor contraction
IEC	Independent Ethics Committee
IPIS	Instillation Procedure Impression Scale
ITT	Intent-to-treat
IRB	Institutional Review Board
IWRS	interactive web response system
KM	Kaplan-Meier

LOCF	last observation carried forward
LS	least squares
MCC	maximum cystometric capacity
NDO	neurogenic detrusor overactivity
NOEL	no observed effect level
OAB	overactive bladder
[redacted]	
PCS	potentially clinically significant
[redacted]	
PPBC	Patient Perception of Bladder Condition
[redacted]	
PSA	prostate-specific antigen
PVR	Post-void residual
$Pdet_{max}$	maximum detrusor pressure
SAE	Serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
UDS	urodynamic studies
UIE	urinary incontinence
UTI	urinary tract infection