NCT03052764

Study ID: CMO-US-URO-0470

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate an Alternative Injection Paradigm for OnabotulinumtoxinA (BOTOX®) in the Treatment of Overactive Bladder in Patients with Urinary Incontinence (LO-BOT).

Protocol Amendment 1: 08 May 2018

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STUDY TITLE

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate an Alternative Injection Paradigm for OnabotulinumtoxinA (BOTOX®) in the Treatment of Overactive Bladder in Patients with Urinary Incontinence (LO-BOT).

Protocol Number:	CMO-US-URO-0470
Amendment, Date:	Amendment 1, 08 May 2018
Phase:	4
Name of Investigational Product:	OnabotulinumtoxinA (BOTOX)
Sponsor:	Allergan (North America) 2525 Dupont Drive Irvine, California 92612 USA

Global Medical Affairs

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

INVESTIGATOR SIGNATURE PAGE

INVESTIGATOR:

STUDY LOCATION:

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.

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

Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date

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[redacted]

Protocol Summary

Study Compound(s): BOTOX® (OnabotulinumtoxinA) Purified Neurotoxin Complex

Phase: IV

Study Objective(s): To evaluate the efficacy and safety of BOTOX 100 U (onabotulinumtoxinA), compared to placebo, when injected into the bladder using an alternative injection paradigm (2 trigonal and 8 peri-trigonal injections) in reducing the number of daily urinary incontinence episodes in patients with overactive bladder (OAB) and urinary incontinence whose symptoms have not been adequately managed with an anticholinergic.

Key Clinical Hypotheses:

- BOTOX 100 U is more effective compared to placebo, when injected into the bladder using the alternative paradigm (2 trigonal and 8 peri-trigonal injections), in reducing the number of daily urinary incontinence episodes from baseline at Week 12.

- BOTOX 100 U has an acceptable/better safety profile, including the risk of incomplete bladder emptying and need for clean intermittent catheterization (CIC), when administered as 10 injections into the lower part of the bladder (2 trigonal and 8 peri-trigonal) of patients with OAB with urinary incontinence.

Study Design

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

Duration: Patients will participate in the study until the following study exit criteria are met:

- Completion of 30 weeks post Randomization/Day 1, and

- If a second injection was received, at least 12 weeks post-treatment follow-up after Treatment 2.

Therefore, for full study participation, patients will be expected to participate in the study for a minimum duration of 25 weeks (ie, if patient qualifies for second treatment at Week 12 clinic visit and proceeds to second treatment) and a maximum duration of approximately 53 weeks (ie, if a patient requested and qualified for Treatment 2 at Week 30, received an injection at Week 34, and completes other study visits at the maximum allowable visit window).

Study Treatment Group: BOTOX 100 U Injection

Control: Placebo (saline) Injection

Dosage/Dose Regimen: All patients will receive a study treatment on Day 1 following fulfillment of all of the Day of Treatment Criteria. An additional treatment may also be administered following fulfillment of pre-specified qualification for Treatment 2 criteria and Day of Treatment Criteria.

Study treatment

Treatment of BOTOX 100 U or placebo will be administered as 10 injections each of 0.5 mL, 8 into the lower portion of the posterior wall of the bladder and 2 into the trigone, via cystoscopy.

Treatment 1:

All eligible patients who meet inclusion/exclusion criteria will receive their first treatment with BOTOX 100 U or placebo after randomization on Day 1. All Day of Treatment Criteria must be fulfilled prior to the injection procedure.

Day of Treatment Criteria:

- Central laboratory urinalysis results and, if applicable, urine culture and sensitivity results for possible urinary tract infection (UTI) from Screening have been reviewed
- Negative urine dipstick reagent strip test (for nitrites and leukocyte esterase (WBC)) on the day of Treatment.
- Patient is asymptomatic for a UTI on the day of treatment, in the opinion of the investigator.
- Patient has discontinued any antiplatelet or anticoagulant therapy or medications with anticoagulative effects 3 days prior to treatment. Some medications may need to be withheld for > 3 days per clinical judgment of the investigator.
- Negative urine pregnancy test for women of childbearing potential on the day of Treatment 1.
- Patient has initiated appropriate antibiotic medication 1 (approximately 24 hours) to 3 days prior to treatment injection, and will continue it on the day of treatment injection, and for 1 to 3 days after treatment injection (see Section 5.9.2 Prophylactic Antibiotics)
- No symptoms or history of bladder stones or bladder malignancies, based on clinical assessment
- Investigator deems study treatment is medically appropriate and no condition or situation exists which, in the investigator's opinion, puts the patient at significant risk from receiving study treatment

Treatment 2:

A second treatment may be administered provided the patient qualifies for Treatment 2 (see below criteria) and only if the Day of Treatment Criteria are fulfilled. All patients will receive BOTOX 100 U for their second treatment. The Qualification for Treatment 2 can occur any time starting at Week 12 up to Week 30 post Treatment 1 and must occur during a clinic visit, either at a regular prescheduled visit or an additional unscheduled visit, depending on the timing of the request for a second treatment. If the patient does not request a second treatment, then the Week 30 clinic visit will be an exit visit.

Qualification for Treatment 2 criteria;

- Patient must initiate request for Treatment 2.
- Patient experiences ≥ 2 episodes of urinary urgency incontinence, with no more than one urgency incontinence-free day, as determined by 3 consecutive days of bladder diary completion in the week prior to the Qualification for Treatment 2 visit.

- Post-void residual (PVR) urine volume must be < 200 mL at the Qualification for Treatment 2 visit.
- Investigator deems that Treatment 2 is medically appropriate and no condition or situation exists which in the investigator's opinion, puts the patient at significant risk from receiving a second treatment.
- A minimum of 12 weeks must have elapsed since Ttreatment 1.

Once these criteria have been met, the patient will be considered qualified for Treatment 2. Treatment 2 administration should occur within 28 days of the Qualification for Treatment 2 visit. The previously described Day of Treatment criteria must be met at the Treatment 2 visit prior to injection.

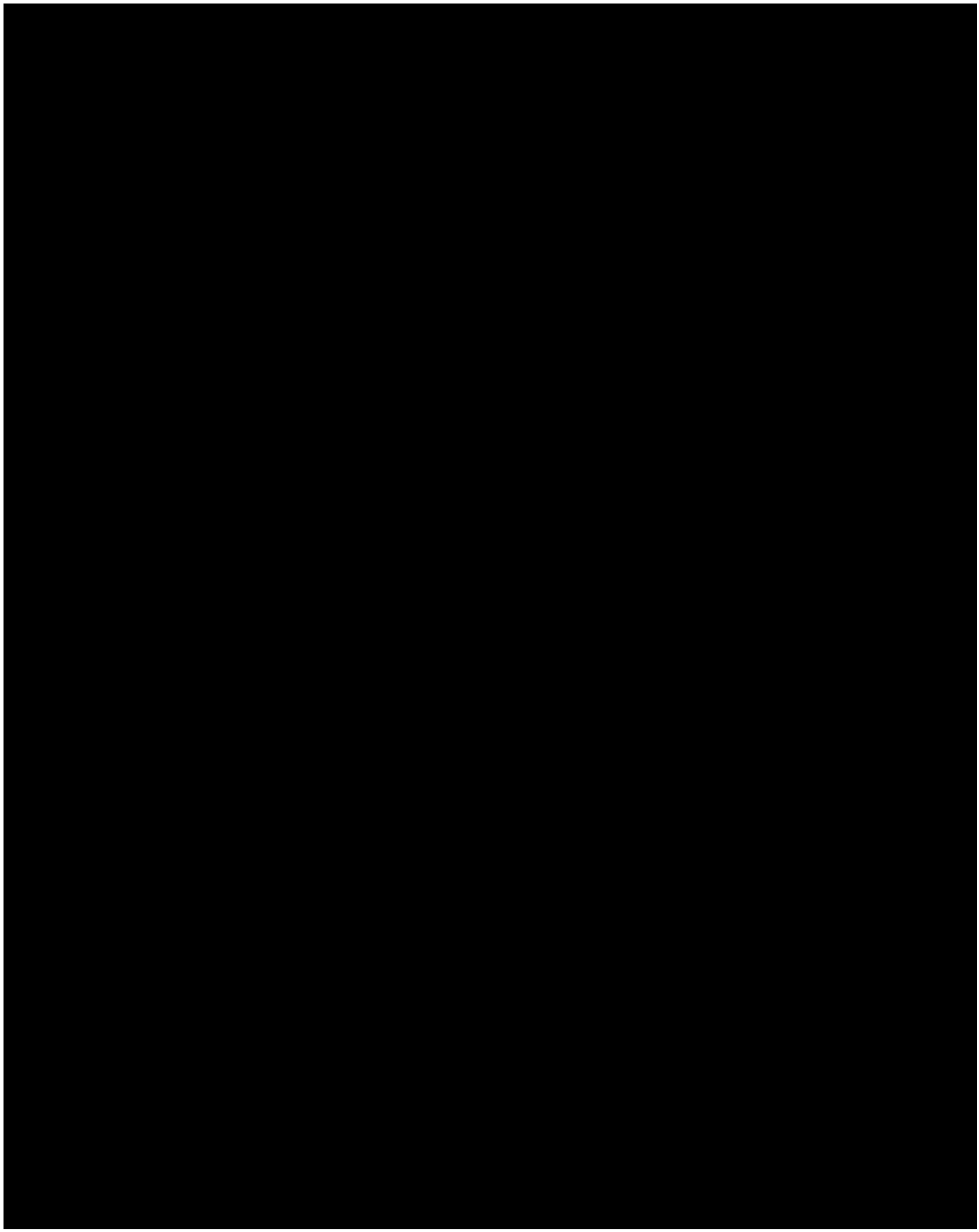
***Randomization*:**

Following the screening period, patients who meet the study inclusion/exclusion criteria will be randomly assigned by an interactive web response system (IWRS) to 1 of 2 treatment arms (BOTOX 100 U or placebo) in a 2:1 ratio. One randomization number will be assigned to each patient prior to the first treatment and will be associated with one of the following treatment arms:

A) BOTOX 100 U

B) Placebo

[redacted]



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Study Population Characteristics

Number of Patients or Subjects: At least 114 patients will be randomized at approximately 50 sites in the United States (US), in order to achieve 68 patients in the BOTOX 100 U treatment group and 34 patients in the placebo treatment group at the primary time point ie, 102 patients at Week 12 are required. At least 114 patients will be randomized to take into account an attrition rate of 10%.

Language: All study materials, whether printed or electronic, including informed consent forms, e-Diary, protocol and all patient and site information will be in the English Language. There are no plans to translate study materials into other languages.

Condition/Disease: Patients with symptoms of OAB (frequency and urgency) and urinary incontinence, whose symptoms have not been adequately managed with an anticholinergic.

Key Inclusion Criteria: The patient must meet the following key criteria at screening and Randomization/Day 1 in order to be included in the study. These are the key criteria which define the population, not a complete list of all inclusion criteria:

- Patient is male or female, aged ≥ 18 years old.
- Patient weighs ≥ 40 kg (88 lbs).
- Patient has symptoms of OAB (frequency and urgency) with urinary incontinence for a period of at least 6 months immediately prior to screening, determined by documented patient history.
- Patient understands that they are not to alter their customary life patterns around fluid consumption or micturition while participating in this study.

[redacted]

[redacted]

Key Exclusion Criteria: The patient will be excluded from participating in the study for any of the following key criteria assessed during the screening period and Randomization/Day 1, prior to study treatment. These are the key criteria which define the population, not a complete list of all exclusion criteria:

- Patient has symptoms of OAB due to any known neurological reason (eg, spinal cord injury, multiple sclerosis, cerebrovascular accident, Alzheimer's disease, Parkinson's disease, etc.).

[redacted]

- Patient has received pharmacologic therapy to treat symptoms of OAB, including nocturia, within 7 days of the start of the screening period procedures.
- Patient uses CIC or indwelling catheter to manage urinary incontinence.
- Patient has a 24-hour total volume of urine voided > 3000 mL, collected over 24 consecutive hours during the 3-day bladder diary collection period prior to Randomization/Day 1.
- Patient has had previous or current botulinum toxin therapy of any serotype for any urological condition.
- Patient has had previous or current botulinum toxin therapy of any serotype for any non-urological condition within 12 weeks prior to Randomization/Day 1.
- Patient has history or evidence of any pelvic or urological abnormalities, bladder surgery or disease, other than OAB, that may affect bladder function including but not limited to:

[redacted]

- Patient has evidence of urethral and/or bladder outlet obstruction, in the opinion of the investigator, at screening or Randomization/Day 1.
- Patient has a PVR urine volume of > 100 mL at screening. The PVR urine volume measurement can be repeated once; the patient is to be excluded if the repeated measure is above 100 mL.

[redacted]

Response Measures

***Efficacy*:**

Primary:

- Change from baseline in number of episodes of urinary incontinence at Week 12 as recorded by the patient in the 3-day bladder diary.

Secondary:

- Proportion of patients who achieve 100% reduction in urinary incontinence episodes (complete continence) from baseline (ie, baseline prior to Treatment 1)
- Change from baseline in daily average number of micturition episodes
- Change from baseline in daily average number of urgency episodes
- Change from baseline in daily average number of nocturia episodes
- Proportion of patients who have a positive treatment response on the TBS (score of either 1 or 2, representing 'greatly improved' or 'improved', respectively).

[redacted]

Safety:

- Adverse events and serious adverse events (SAEs)
- Physical examination
- Vital signs
- PVR urine volume (by bladder scan or ultrasound)
- Pregnancy test for women of childbearing potential (at screening, before study treatment(s) and at study exit)
- Urine dipstick reagent strip test
- Central laboratory urine analysis
- Urine culture and sensitivity
- Concomitant medications
- Concurrent procedures (including catheterization with associated frequency and reason for catheterization).

General Statistical Methods and Types of Analyses: Efficacy endpoints will be analyzed using the modified intent-to-treat (mITT) Population. The primary efficacy endpoint is the change from baseline at Week 12 in the daily average number of episodes of urinary incontinence, as recorded in the 3-day bladder diary.

Comparison of BOTOX 100 U and placebo at Week 12 for the primary efficacy endpoint and other continuous endpoints will be performed using analysis of covariance with treatment as a factor, and baseline value and the number of urgency incontinence episodes reported at baseline (≤ 9 or > 9 daily episodes, over the 3-day bladder diary at baseline) as covariates. The 95% confidence interval (CI) for the least squares (LS) mean difference between BOTOX 100 U and placebo will be constructed.

Comparison of BOTOX 100 U and placebo at Week 12 for the proportion of patients with 100% reduction in urinary incontinence episodes from baseline and other categorical endpoints will be analyzed using Cochran Mantel-Haenszel (CMH) method with the number of urgency incontinence episodes reported at baseline (≤ 9 or > 9 daily episodes, over the 3-day bladder diary at baseline) as another categorical factor. The 95% CI for the odds ratio of BOTOX 100 U over placebo will be constructed.

Safety endpoints (including adverse events, laboratory urine data, vital signs, and PVR urine volume) will be summarized descriptively by treatment based on the Safety Population.

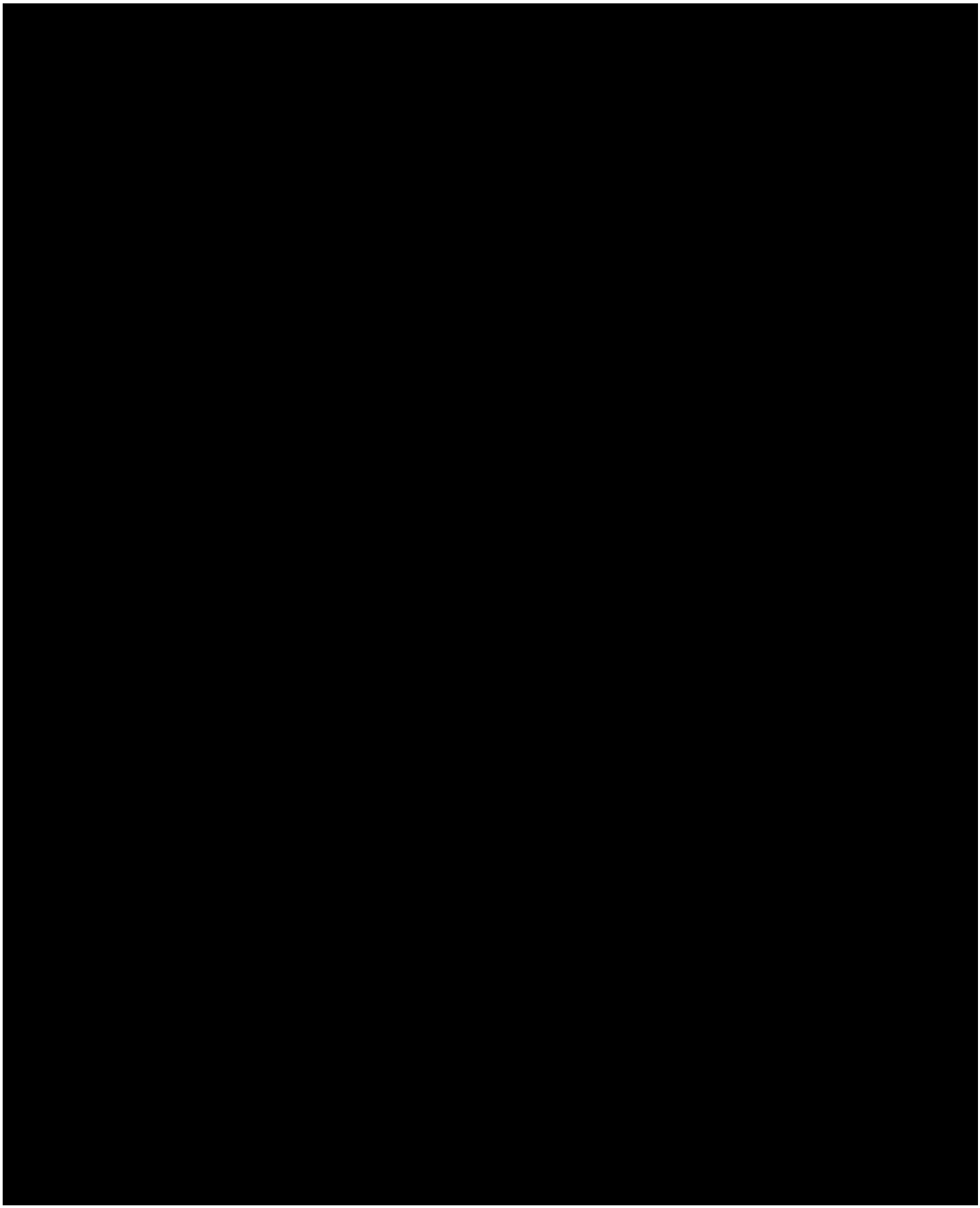
Sample Size Calculation:

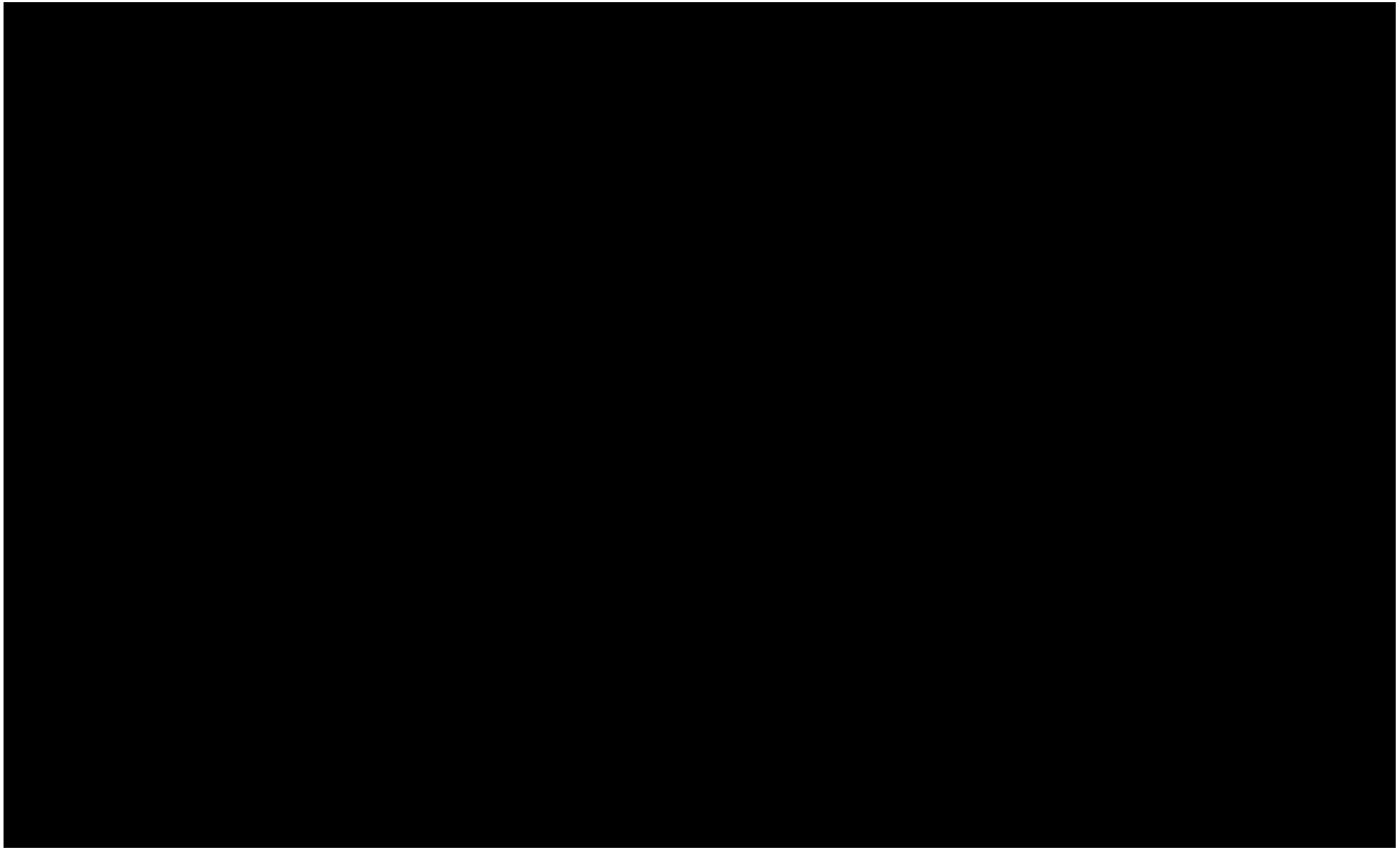
The assumptions used for sample size calculation are from the Phase III pivotal studies (191622-095 and 191622-520) results.

Assuming a mean and standard deviation of change from baseline at Week 12 in the number of urinary incontinence episodes are -2.8 (±3.45) and -0.95 (±2.9) for BOTOX 100 U and placebo, respectively, this study requires 102 patients (68 BOTOX patients and 34 placebo patients) to provide 80% power for detecting a significant difference of the primary efficacy endpoint (change from baseline in number of urinary incontinence episodes at Week 12) at a significance level (alpha) of 5% using a 2-sided z-test at the end-of-study analysis.

With 10% dropout rate , the sample size required for the patients to be randomized in the study will be approximately 114 patients.

[redacted]





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1. Background and Clinical Rationale

Overactive Bladder and Urinary Incontinence

Overactive bladder (OAB) syndrome is a symptom-based diagnosis and is defined as urgency, with or without urgency incontinence, usually with frequency and nocturia (Abrams et al, 2002). These symptoms are a consequence of the bladder's inability to effectively store urine due to an underlying dysfunction in the coordinated mechanisms that provide controlled storage and voiding of urine. However, in the absence of a known neurological insult or pathophysiological cause, the reason for dysfunction is unknown in the majority of cases resulting in the condition known as idiopathic OAB.

Epidemiology and Impact of Overactive Bladder

OAB is a prevalent disorder that is reported to affect between 12% and 17% of the general population in North America and Europe (Milsom et al, 2001; Stewart et al, 2003; Irwin et al, 2006; Herschorn et al, 2008), with a similar prevalence also being reported in Asia and South America (Homma et al, 2005; Yu et al, 2006; Teloken et al, 2006). Overall, approximately one third of OAB patients have OAB with urinary urgency incontinence, or 'wet OAB' (Irwin et al, 2006). Both OAB and 'wet' OAB increase with advancing age, and the rate of increase 'wet' OAB with age is greater in women than men (Milsom et el, 2001; Tubaro, 2004). Urinary incontinence carries a considerable social stigma and many sufferers are unable to continue with their activities of daily living or are unable to continue with employment.

Currently Available Therapy

Therapy for OAB focuses on the symptomatic relief of patient symptoms. Treatment for OAB typically begins with bladder training, pelvic floor muscle training, and lifestyle advice. Pharmacological therapy is generally limited to the use of anticholinergic agents and recently beta-3 agonists. However, the utility of oral medicines can be limited by inadequate efficacy or intolerable side effects, such as dry mouth, constipation, or cognitive deficits (Chapple et al, 2008). This often results in poor treatment compliance by the patient and cessation of treatment by physicians (Lawrence et al, 2000; Kreder et al, 2002). Analysis of a database containing information from 29,369 women prescribed anticholinergics for lower urinary tract symptoms in the United Kingdom reported discontinuation rates of 59% by 6 months (Gopal et al, 2008). The overall 'switch rate' to another anticholinergic was low at 15%; however, in a subset of patients there was a high switch rate (approximately 60%),

which the authors suggested represents patients with severe symptoms who are still willing to try new medications in order to achieve relief from their condition.

There are few second-line treatment options available for patients with OAB who do not have sufficient benefit with oral therapies. Surgical implantation of sacral nerve stimulation/neuromodulation systems is an option; however, the nature of this intervention means that reoperation is required due to the limited longevity of the neurostimulator (Starkman et al, 2010). In addition to battery wear or lack of effect, reoperation or explanation can also occur for various reasons such as lead migration, infection, or pain at the stimulator site (Hijaz et al, 2006; Starkman et al, 2010). Peripheral tibial nerve stimulation (PTNS) for OAB treatment involves the percutaneous placement of a needle electrode in the medial malleolus of the ankle which then delivers an electrical stimulation of the posterior tibial nerve. At least weekly sessions of 30 minutes are required in the initial months, as well as subsequent maintenance sessions (Peters et al, 2010; MacDiarmid et al, 2010). The durability of response is uncertain following PTNS and there is limited controlled data with this type of device in the OAB population (Starkman et al, 2010).

For patients with intractable symptoms, the only remaining option is major reconstructive surgery such as augmentation cystoplasty with the aim of increasing the capacity of the bladder. In addition to the risk of a major surgical procedure, complications such as metabolic disorders and chronic retention are common, and these procedures do not guarantee continence.

The recent approval of BOTOX (onabotulinumtoxinA) in adults with OAB who have had an inadequate response to an anticholinergic has added an important second line prescription treatment option for this population .

BOTOX Development Program

The Allergan clinical development program for BOTOX in patients with OAB and urinary incontinence was initiated with a phase II study (191622-077) that evaluated a range of BOTOX doses (50, 100, 150, 200, and 300 U) versus placebo. A total of 313 patients were enrolled and the study showed improvements in OAB symptoms and urodynamic parameters at doses of 100 U and above. This was also reflected in consistent improvements in health-related quality of life (HRQOL) at doses of 100 U and above. A dose-dependent safety profile was identified with respect to adverse events of urinary retention and urinary tract infection (UTI), as well as in post-void residual (PVR) urine volume and use of clean

intermittent catheterization (CIC). The dose of 100 U was evaluated as providing the appropriate benefit/risk balance in the target population.

A phase III program was subsequently initiated that included 2 identical double-blind, randomized, pivotal phase III studies (Studies 191622-095 Nitti et al 2013; and 191622-520 Chapple et al. 2013), both of which evaluated a dose of BOTOX 100 U compared to placebo. A total of 1105 patients were enrolled in the pivotal studies. Both of these phase III pivotal studies assessed patients for at least 24 weeks, with the opportunity for retreatment with BOTOX 100 U if prespecified retreatment criteria were met from 12 weeks onwards. The co-primary measures in both studies were the number of episodes of urinary incontinence and the proportion of responders on the Treatment Benefit Scale (TBS), defined as patients who rated their perception of response to treatment as either 'greatly improved' or 'improved' compared to baseline. The primary timepoint was Week 12 following the first study treatment.

Both pivotal phase III studies, 191622-095 and 191622-520, achieved a statistically significant and clinically relevant treatment effect of BOTOX 100 U, and results were consistent between the 2 studies. The co-primary efficacy endpoints were met in both studies ($p < 0.001$), with clinically meaningful reductions from baseline in urinary incontinence and clear patient perception of improvement in their condition using the TBS. Furthermore, all secondary endpoints were met in both studies, which included OAB symptoms and HRQOL parameters. Specifically, BOTOX 100 U attenuated all OAB symptoms; thus a significant treatment effect was observed for urinary incontinence, micturition frequency, urgency, and nocturia. The improved ability of the bladder to store urine was reflected in significant increases in volume voided per micturition. Similarly, the secondary endpoints of change from baseline in the Incontinence Quality of Life total summary score and the change from baseline in the 2 multi-item King's Health Questionnaire (KHQ) domain scores 'Role Limitations' and 'Social Limitations' at Week 12 were also met ($p < 0.001$).

In terms of safety, adverse events that were higher following BOTOX treatment compared to placebo were primarily limited to local adverse events related to the urinary tract, in particular UTI, bacteriuria, dysuria, and urinary retention. A dose-dependent increase in PVR urine volume was observed post treatment, and a proportion of those patients initiated CIC. However, the proportion of patients with a change from baseline PVR urine volume ≥ 200 mL at any time during treatment was low (less than 9% in both studies), and correspondingly, the proportion of patients who initiated CIC was also low (6.5%).

Patients who were enrolled in the pivotal phase III studies had the opportunity of enrolling into a long-term follow-up study, 191622-096. This study has been completed (N=839), and patients will participate in the follow-up study for up to an additional 3 years and receive only active treatment (on fulfillment of Qualification and Day of Treatment Criteria). The final analysis of this extension study demonstrated a consistent efficacy and safety profile over repeated BOTOX treatments.

As the use of BOTOX has evolved over the past few years after marketing approval, more data have emerged on the efficacy and risks of BOTOX use. The established scientific data describing the enervation and contractility of the bladder, coupled with better understanding of the mechanism of action of BOTOX on the sensory enervation has led to a hypothesis that is the basis for this study. Based on these emerging data as well as many unpublished anecdotal reports, injecting BOTOX into the lower portion of the bladder and trigone may have a more profound effect on the afferent portion of the OAB complex without markedly affecting the normal functions of the bladder musculature during normal voiding. This hypothesis postulates that by altering the injection paradigm of BOTOX in OAB patients, similar efficacy to that of the current paradigm could be achieved while reducing the risk of partial urinary retention requiring CIC in those patients.

The purpose of this study is to test the above hypothesis by evaluating the efficacy and safety of an alternative injection paradigm for BOTOX 100 U with respect to occurrence of urinary incontinence episodes in patients with OAB and its impact on their quality of life (QOL).

2. Study Objectives and Clinical Hypotheses

2.1 Study Objectives

The primary objective of this study is to evaluate the efficacy and safety of BOTOX 100 U (onabotulinumtoxinA), compared to placebo, when injected into the bladder using an alternative injection paradigm (2 trigonal and 8 peri-trigonal injections) in reducing the number of daily urinary incontinence episodes in patients with OAB and urinary incontinence whose symptoms have not been adequately managed with an anticholinergic.

The secondary objectives of this study are to evaluate the QOL impact, duration of treatment effect, early onset of treatment effect, and safety of BOTOX (100 U) in patients with OAB and urinary incontinence whose symptoms have not been adequately managed with an anticholinergic.

2.2 Clinical Hypotheses

BOTOX 100 U is more effective compared to placebo, when injected into the bladder using the alternative paradigm (2 trigonal and 8 peri-trigonal injections), in reducing the number of daily urinary incontinence episodes from baseline at Week 12.

BOTOX 100 U has an acceptable/better safety profile, including the risk of incomplete bladder emptying and need for clean intermittent catheterization (CIC), when administered as 10 injections into the lower part of the bladder (2 trigonal and 8 peri-trigonal) of patients with OAB with urinary incontinence.

BOTOX 100U administered into 10 injection sites limited to the lower portion of the bladder (alternative paradigm) rather than 20 sites in the posterior wall is effective in achieving efficacy in patients with OAB while reducing the risk of incomplete bladder emptying in those patients.

BOTOX 100 U, administered using an alternative injection paradigm, is effective for longer duration than placebo as assessed by the difference between treatment groups in the time to qualification for second treatment (qualification for Treatment 2 criteria provided in Section 5.10.1 Request/Qualification for Treatment 2) during the 30 weeks of follow-up after the first treatment injection.

3. Study Design

This will be a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the safety and efficacy of a single treatment of BOTOX, administered using an alternative injection paradigm, followed by a second treatment (if applicable) with BOTOX in patients with OAB with urinary incontinence whose symptoms have not been adequately managed with an anticholinergic.

Following the screening period, patients meeting the study inclusion/exclusion criteria will be randomly assigned by an interactive web response system (IWRS) to 1 of 2 treatment arms (BOTOX 100 U or placebo) in a ratio of 2:1. A central randomization scheme will be utilized. The overall enrollment period may be up to 24 months.

Patients will be eligible to receive a second treatment if all the predefined Treatment 2 criteria are met (see Section 5.10.2). All patients will receive BOTOX 100 U for Treatment 2. One randomization number will be assigned to each patient prior to the first treatment and will be associated with one of the following treatment arms:

A) BOTOX 100 U (Treatment 1)/BOTOX 100 U (Treatment 2 if qualified)

B) Placebo (Treatment 1)/BOTOX 100 U (Treatment 2 if qualified)

Patients will be followed regularly for safety and efficacy at post-treatment visits. Patients will complete up to 2 treatments with a minimum full study participation of 25 weeks (ie, if patient requests a second treatment at Week 12 and qualifies for second treatment) and a maximum duration of approximately 53 weeks (ie, if a patient qualifies for Treatment 2 at Week 30, receives an injection at Week 34, and completes other study visits at the maximum allowable visit window).

4. Study Population and Entry Criteria

4.1 Number of Subjects

At least 114 patients will be randomized at approximately 50 sites in the United States (US), in order to achieve 68 patients in the BOTOX 100 U treatment group and 34 patients in the placebo treatment group at the primary time point ie, 102 patients at Week 12 are required. At least 114 patients will be randomized to take into account an attrition rate of 10%.

4.2 Study Population Characteristics

The study will include patients with symptoms of OAB (frequency and urgency) with urinary incontinence, whose symptoms have not been adequately managed with an anticholinergic. For the purposes of this protocol, 'not adequately managed' is defined as an inadequate response after receiving an anticholinergic for at least 4 weeks on an optimized dose(s) (ie, patient is still incontinent despite use of an anticholinergic) or limiting side effects after receiving an anticholinergic for at least 2 weeks on an optimized dose(s).

4.3 Inclusion Criteria

To be included in the study, the patient must meet the following criteria at screening and Randomization/Day1, prior to study treatment.

1. Written informed consent has been obtained.
2. Written Authorization for Use and Release of Health and Research Study Information has been obtained.

3. Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable.
4. Patient is male or female, aged ≥ 18 years old.
5. Patient weighs ≥ 40 kg (88 lb).
6. Patient has symptoms of OAB (frequency and urgency) with urinary incontinence for a period of at least 6 months immediately prior to screening, determined by documented patient history.

[redacted]

4.4 Exclusion Criteria

Patients will be excluded from participating in the study for any of the following criteria assessed during the screening period and Randomization/Day 1, prior to study treatment:

1. Patient has symptoms of OAB due to any known neurological reason (eg, spinal cord injury, multiple sclerosis, cerebrovascular accident, Alzheimer's disease, Parkinson's disease, etc.).

[redacted]

3. Patient has received pharmacologic therapy to treat symptoms of OAB, including nocturia, within 7 days of the start of the screening period procedures.
4. Patient uses CIC or indwelling catheter to manage urinary incontinence.
5. Patient has been treated with any intravesical pharmacologic agent (eg, capsaicin, resiniferatoxin) within 12 months of Randomization/Day 1.
6. Patient has had previous or current botulinum toxin therapy of any serotype for any urological condition.
7. Patient has had previous or current botulinum toxin therapy of any serotype for any non-urological condition within 12 weeks of Randomization/Day 1.
8. Patient has been immunized for any botulinum toxin serotype.
9. Patient has history or evidence of any pelvic or urological abnormalities, bladder surgery or disease, other than OAB, that may affect bladder function including but not limited to:

[redacted]

11. Patient has an active genital infection, other than genital warts, either concurrently or within 4 weeks prior to screening.

12. Patient has a history or current diagnosis of bladder cancer or other urothelial malignancy, [redacted]

13. Patient is male with previous or current diagnosis of prostate [redacted]

[redacted]

18. Patient has a history of 2 or more UTIs within 6 months of Randomization/Day 1 or is taking prophylactic antibiotics to prevent chronic UTIs.

[redacted]

20. Patient has current or previous uninvestigated hematuria. [redacted]

21. Patient has hemophilia, or other clotting factor deficiencies, or disorders that cause bleeding diathesis.

22. Patient cannot withhold any antiplatelet, anticoagulant therapy or medications with anticoagulant effects for 3 days prior to Randomization/Day 1. [redacted]

23. Patient has a known allergy or sensitivity to any botulinum toxin preparation [redacted]

24. Patient has any medical condition that may put him/her at increased risk with exposure to BOTOX including diagnosed myasthenia gravis, Eaton-Lambert syndrome, or amyotrophic lateral sclerosis.

25. Patient has current swallowing or breathing difficulties.

[redacted]

4.5 Permissible and Prohibited Medications/Treatments

4.5.1 Permissible Medications/Treatments

Therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. Patients should be instructed to maintain a stable dose during the study, whenever possible. All medications and adjunct therapies should be recorded on the appropriate electronic case report form (eCRF).

Where the independent review board (IRB) does not agree to permitting the temporary discontinuation of anticoagulant/antiplatelet medications then patients using these medications will not be consented, and are excluded from the study.

For sites under jurisdiction of a local IRB, where applicable, anticoagulant medications maybe temporarily discontinued (eg, warfarin and other coumadin derivatives), antiplatelet medications (eg, clopidogrel and aspirin [including low dose]) and any other medications with anticoagulative effects (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]). These medications are prohibited for a minimum of 3 days (or longer according to the clinical judgment of the investigator) prior to study treatment injections, and must not be recommenced until the day following any injection, the use of low molecular weight heparins (eg, enoxaparin) is permitted up to 24 hours prior to the injections, if medically indicated.

Use of antihistamines and/or decongestants (sympathomimetics to treat upper respiratory infections or allergies) is permitted up to 48 hours prior to the day of injection, and may be resumed the day following treatment.

Refer to Section 5.9.4 Treatment Procedure for information on permitted study treatment anesthesia.

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

4.5.1.1 Definition of Females of (Non-) Childbearing Potential and/or Acceptable Contraceptive Methods

A woman of no childbearing potential is defined as a female who is either postmenopausal (at least 12 months) and/or who is without a uterus or both ovaries.

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

The investigator and each patient will determine the appropriate method of contraception for the patient during the participation in the study.

If a woman becomes pregnant during participation in the study, the pregnancy is to be reported to Allergan (see Section 9.4 Procedure for Reporting Pregnancy).

4.5.2 Prohibited Medications/Treatments

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

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

Pharmacologic therapy (including sympathomimetic medications) used for the treatment of symptoms of OAB, including nocturia are prohibited within 7 days of the start of the screening procedures and throughout study participation.

Muscle relaxants are prohibited on the day of treatment injection with no other prior washout, and can be resumed the day following injection. Administration of intravesical capsaicin or resiniferatoxin is prohibited during the study.

Use of electrical stimulation and neuromodulation devices (implanted and external) for the treatment of OAB is prohibited during study participation (if a patient is enrolled into the study with a device still implanted, it must be inactive 4 weeks prior to Randomization/Day 1 and for the duration of the study).

Use of aminoglycoside antibiotic therapy is not permitted during study treatment administration. If a patient requires aminoglycoside antibiotic therapy during the trial, any study treatment administration must be delayed until the aminoglycoside antibiotic therapy is completed. Caution is advised if the patient requires treatment with an aminoglycoside antibiotic or curare-like agent during the course of the study. This is due to the potential interaction of these treatments with BOTOX at the neuromuscular junction and may therefore result in an unpredictable effect on the detrusor muscle. Use of aminoglycoside antibiotics should also be avoided for 8 weeks after study treatment (refer also to Section 5.9.2 Prophylactic Antibiotics).

Anticoagulant medications (eg, warfarin and other coumadin derivatives), antiplatelet medications (eg, clopidogrel and aspirin [including low dose]) and any other medications with anticoagulative effects (eg, NSAIDs) are prohibited for a minimum of 3 days (or longer according to the clinical judgment of the investigator) prior to study treatment injection, and must not be recommenced until the day following injection (see Section 4.5.1).

5. Study Treatments

5.1 Study Treatment and Formulation

BOTOX

[redacted]

5.2 Control Treatment

BOTOX Placebo (Saline)

[redacted]

5.3 Methods for Masking/Blinding

The injectable investigational materials will be packaged and labeled in identically appearing vials. The study treatments will be identified as an investigational compound. The study number and kit number will be identified on the unit label.

Patients, investigators, study site staff, sponsor and their designees will be blinded to treatment assignments. Procedures for breaking the blind for a patient, should it be necessary for safety reasons, are provided in Section 9.5.

5.4 Treatment Allocation Ratio

Patients will be randomly assigned by an IWRS, using a computer-generated random code list, to 1 of 2 treatment arms (BOTOX 100 U or placebo) in a 2:1 ratio. A central randomization scheme will be utilized. One randomization number will be assigned to each patient prior to the first treatment and will be associated with one of the following treatment groups:

- BOTOX 100 U
- placebo

5.5 Method for Assignment to Treatment Groups/Randomization

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

Following the screening period, patients who meet the study inclusion/exclusion criteria and Day of Treatment Criteria will be assigned a randomization number through the IWRS that determines the treatment group assignment. The study medication will be labeled with unique kit numbers. The IWRS will provide the site with specific medication kit numbers for the patient that corresponds to the treatment group to which the patient was assigned. The

site will also use IWRS to assign a new kit number to each patient who meets Treatment 2 criteria.

5.6 Treatment Regimen and Dosing

5.6.1 Study Treatments

BOTOX

[redacted]

Study Treatment 1

All eligible patients who meet inclusion/exclusion criteria and are enrolled into the study will receive a double-blind treatment of either BOTOX 100 U or placebo for their first study treatment.

The first treatment will be administered after randomization on Day 1 at the investigational site. All Day of Treatment Criteria must be fulfilled prior to treatment administration (see Section 5.9.1 Day of Treatment 1 Criteria).

Study Treatment 2

All patients can request and potentially qualify for a second treatment, and if the qualification criteria are met (Qualification for Treatment 2 Criteria provided in Section 5.10.1 Request/Qualification for Treatment 2) they will receive BOTOX 100 U for their second treatment.

Administration of Treatment 2 should occur within 28 days of the qualification for Treatment 2 visit. Patients must fulfill the 'Day of Treatment 2 Criteria' prior to Treatment 2 administration (see Section 5.10.2 Day of Treatment 2 Criteria). Treatment 2 must not be administered before 12 weeks after Treatment 1.

The reason(s) for the patient requesting retreatment will be collected at each visit in which the request is made, regardless of whether the patient qualifies for Treatment 2 at that visit or not.

5.7 Storage of Study Medications/Treatments

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

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

5.8 Preparation/Dispensing of Study Medications

The vacuum-dried injectable study medication will be prepared from the assigned medication kit number. An independent drug reconstituter (IDR) will be responsible for drug reconstitution and will not have any other involvement in the study as they will be unblinded. Instructions for the reconstitution and preparation of the injectable study medication are provided in the Pharmacy Manual and in Attachment 12.1 Preparation of Study Medication.

5.9 Study Medication Administration

5.9.1 Day of Treatment 1 Criteria

The following 'Day of Treatment 1 Criteria' must be fulfilled prior to the administration of study medication on Day 1:

- Central laboratory urinalysis results and, if applicable, urine culture and sensitivity results from screening for possible UTI have been reviewed.

- Negative urine dipstick reagent strip test (for nitrites and leukocyte esterase (WBC)) on the day of treatment
- Patient is asymptomatic for a UTI on the day of treatment, in the opinion of the investigator.
- Patient has discontinued any antiplatelet or anticoagulant therapy or medications with anticoagulative effects at least 3 days prior to treatment. Some medications may need to be withheld for > 3 days per clinical judgment of the investigator (see Section 4.5.1)..
- Patient has initiated appropriate antibiotic medication 1 (approximately 24 hours) to 3 days prior to treatment injection, and will continue it on the day of the treatment injection, and for 1 to 3 days after the treatment injection (see Section 5.9.2)
- Negative urine pregnancy test for women of childbearing potential on the day of treatment
- No symptoms or history of bladder stones or bladder malignancies, based on clinical assessment
- Investigator deems study treatment is medically appropriate and no condition or situation exists which, in the investigator's opinion, puts the patient at significant risk from receiving study treatment.

5.9.2 Prophylactic Antibiotics

Prophylactic antibiotics are to be administered beginning 1 (approximately 24 hours) to 3 days before study treatment, on the day of study treatment, and continuing for 1 to 3 days after study treatment. The investigator is to prescribe the appropriate antibiotic and number of days pretreatment and post treatment based on clinical judgment and local site practice.

5.9.3 Use of Anesthesia

The use of anesthesia during study treatment administration is determined by the investigator.

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

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

The following are the only anesthesia options that are permitted during study treatment administration:

- local anesthesia to the bladder wall
    - instillation into the bladder of 1 to 2% lidocaine (or similar acting local anesthetic) prior to the procedure
    - the instillation solution should remain in the bladder for at least 15 minutes in order to achieve sufficient anesthesia
    - the bladder will then be drained of lidocaine, rinsed with saline, and drained again
- sedatives may also be administered according to local site practice if deemed medically necessary

5.9.4 Treatment Procedure

A flexible or rigid cystoscope may be used for study treatment administration. As described in Section 5.9.3, lubricating gel and intraurethral lidocaine (or similar) can be used to facilitate cystoscope insertion. The bladder should be instilled with a sufficient amount of saline in order to achieve adequate visualization for the study injections.

The investigator will receive one 5-mL syringe prefilled with 5 mL of study medication, and one 1-mL syringe prefilled with saline. The 5 mL of study drug (100 U) will be administered as 10 injections each of 0.5 mL.

Ten injections of study medication are to be made under direct cystoscopic visualization, with 8 injections distributed evenly across the posterior wall of the bladder around the trigonal area and spaced approximately 1 cm apart and 2 injections into the trigone approximately 1 cm apart and avoiding the ureteric opening (see Attachment 12.2 Study Treatment Alternative Injection Pattern). The injection needle should be filled (primed) with approximately 1 mL of reconstituted study medication prior to the start of the injections (depending on needle length) to remove any air. The injection needle should be inserted approximately 2 mm for each injection. For the final injection site, a sufficient amount of saline (from the 1-mL syringe) will be flushed through the injection needle to deliver the small amount of study medication remaining in the needle. This will ensure that the entire volume of study medication is delivered to the patient.

After the injections are given, the saline used for visualization should not be drained from the bladder, so that patients may demonstrate their ability to void prior to leaving the clinic. Patients should remain in the clinic under observation for at least 30 minutes and until a spontaneous void has occurred. Safety monitoring and assessments are to be done according to local site practice (eg, monitoring of blood pressure, pulse rate). Prior to leaving the study

clinic, patients will be instructed to contact the study site if they experience any adverse events post treatment.

The investigator, or designee, will be required to document on the study treatment eCRF whether the study drug administration was performed as indicated above.

5.10 Retreatment

5.10.1 Request/Qualification for Treatment 2

Patients may request Treatment 2 at the Week 12 clinic visit or any time thereafter up to Week 30. A qualification visit will be added to the patient's schedule if the request for retreatment is made outside the regular prescheduled visits. A clinic visit (prescheduled or unscheduled) at which the patient is assessed after making a request for a second treatment will then become a Qualification for Treatment 2 visit, and is no longer considered the post-treatment visit, and the appropriate eCRFs should be completed. Treatment 2 should occur within 28 days of qualification and no later than Week 34 (+/-7 days). The patient must meet all qualification criteria before Treatment 2 can occur.

The 'Qualification for Treatment 2 Criteria' are:

- Patient must initiate request for Treatment 2
- Patient experiences ≥ 2 episodes of urinary urgency incontinence, with no more than 1 urgency incontinence-free day, as determined by the 3 consecutive days of bladder diary completion in the week prior to the qualification for Treatment 2 visit (ie, Week 12, 24 or 30 post Treatment 1 or an additional visit, depending on the timing of the retreatment request).
- PVR urine volume must be < 200 mL.
- Investigator deems that Treatment 2 is medically appropriate and no condition or situation exists which, in the investigator's opinion, puts the patient at significant risk from receiving a second treatment.
- A minimum of 12 weeks must have elapsed since Treatment 1.

Once a patient has met the 'Qualification for Treatment 2 Criteria', the patient is considered qualified for Treatment 2 and may proceed with the treatment visit (see Section 5.10.2). The Treatment 2 visit may occur on the same day of qualification or may be scheduled on another day if the Treatment 2 criteria are not met. If the Treatment 2 visit is rescheduled, visit procedures for which the patient has already been qualified do not need to be repeated.

5.10.2 Day of Treatment 2 Criteria

A patient should be treated within 28 days of the Qualification for Treatment 2 visit, once all Treatment 2 criteria are met. If the patient does not meet all Treatment 2 criteria at the time of the visit, the treatment visit may be rescheduled within the 28-day window to allow for treatment criteria to be met.

The 'Day of Treatment 2 Criteria' are:

- Urine culture and sensitivity results for possible UTI have been reviewed from Qualification, if applicable.
- Negative urine dipstick reagent strip test (for nitrites and leukocyte esterase (WBC)).
- Patient does not have a UTI.
- Appropriate prophylactic antibiotic coverage has been initiated, and patient understands to continue the antibiotics following the procedure (see Section 5.9.2 Prophylactic Antibiotics)
- Antiplatelet or anticoagulant therapy or medications with anticoagulative effects have been discontinued at least 3 days prior to study treatment (see Section 4.5.1)..
- Negative urine pregnancy test result (for women of childbearing potential)
- Investigator continues to deem study treatment is appropriate and no condition or situation exists which, in the investigators opinion, puts the patient at significant risk from receiving Treatment 2.

Note: Urine culture and sensitivity results need to be available and required prophylactic antibiotics need to have been initiated before Treatment 2 is administered (please refer to Section 5.9.2).

6. Response Measures and Summary of Data Collection Methods

6.1 Efficacy Measures

6.1.1 Primary Measure

The primary efficacy measure is:

- Change from baseline in number of episodes of urinary incontinence at Week 12 as recorded by the patient in the 3-day bladder diary.

6.1.2 Secondary Measures

- Proportion of patients who achieve 100% reduction in urinary incontinence episodes (complete continence) from baseline (ie, baseline prior to Treatment 1)
- Change from baseline in daily average number of micturition episodes
- Change from baseline in daily average number of urgency episodes
- Change from baseline in daily average number of nocturia episodes
- Proportion of patients who have a positive treatment response on the TBS (score of either 1 or 2, representing 'greatly improved' or 'improved', respectively; see Attachment 12.6 for information on completion of this questionnaire).

[redacted]

6.2 Safety Measures

- Adverse events and serious adverse events (SAEs)
- Physical examination
- Vital signs
- PVR urine volume (by bladder scan or ultrasound)
- Pregnancy test for women of childbearing potential (at screening, before study treatment[s] and at study exit)
- Urine dipstick reagent strip test
- Central laboratory urine analysis

- Urine culture and sensitivity
- Concomitant medications
- Concurrent procedures (including catheterization with associated frequency and reason for catheterization)

6.3 Examination Procedures, Tests, Equipment, and Techniques

Patients who have signed an informed consent form and have met the required inclusion and exclusion criteria at the end of the screening period and at Randomization/Day 1 will be randomized and considered enrolled in the study.

Evaluations should be performed by the same evaluator throughout the study whenever possible. If it is not possible to use the same evaluator to follow the patient, then it is preferable to have the evaluations overlap (examine the patient together and discuss findings) for at least 1visit.

6.3.1 Medical History

The patient's history of OAB and other medical history (including diagnosis or symptom, date of onset, current status) and associated surgical procedures (including name of procedure and date of surgery) will be documented, as well as history of the number of UTIs occurring over the past 6 months.

6.3.2 Physical Examination

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

The patient's height and weight will be recorded (height will be recorded at screening only).

6.3.3 Vital Signs

Vital signs will be measured prior to any invasive procedures as outlined below.

Pulse rate (beats per minute): patients should be resting in a seated position. Pulse rate is then counted over 30 seconds and multiplied by 2.

Blood pressure (mm Hg): patients should be resting in a seated position. Systolic/diastolic blood pressure is then measured with a sphygmomanometer.

Temperature (ºF or ºC): patients should be seated and the body temperature taken according to local site practice.

6.3.4 Bladder Diary

All patients will be provided a e-Diary in which to record electronically 3 consecutive days of required bladder diary information. Prior to receiving the e-Diary, patients will be instructed and trained on the use of the electronic diary and the data to be collected. Patients will be required to collect bladder diary data over 3 consecutive 24-hour periods during the week prior to scheduled clinic visits (for screening period only, the diary can be completed for 3 consecutive 24-hour periods at any time during the screening period). Patients must bring the e-Diary to each clinic visit. The electronic diary will capture the following information (terms used on the diary will be patient friendly):

- date and time of urinary episode
- episodes of micturition (toilet voids)
- episodes of urinary incontinence
- episodes of urgency
- episodes of nocturia (voids that awaken from normal sleep)
- start and stop date of CIC
- volume of each void measured over one 24-hour period during the 3-day bladder diary collection period. This will be used to calculate the volume voided per voiding episode (see Section 6.3.5 Total Volume Voided).

More detailed instructions on the use of the e-Diary and completion of the electronic patient bladder diary will be provided to the patient.

The electronic diary data will also be used to satisfy eligibility requirements for study entry, as well as to qualify the patient for Treatment 2.

6.3.5 Total Volume Voided

The total volume of voided urine will be measured by all patients over one 24-hour period during the 3-day bladder diary collection period. Urine collection containers needed to perform this measurement will be supplied to the patients by the sites. Patients are to

measure the volume of each void (voluntary or catheterization) as it occurs and enter that amount (with time of void) into their diary.

6.3.6 Full Bladder Volume and Post-void Residual Urine Volume

The investigator should assess the PVR urine volume measured at the screening visit to determine whether in his/her judgment, the patient should be using CIC to empty the bladder even if currently not doing so. In such cases, the patient should not be considered for entry into the study.

Full bladder volume (screening only) and PVR urine volume (screening and post treatment) are assessed by ultrasound or bladder scan before and after the patient has performed a voluntary void. If a patient is using CIC post treatment, the PVR urine volume will be measured after the patient has attempted to void voluntarily and prior to any catheterization (patients should not have catheterized at least 60 minutes prior to the measurement of the PVR urine volume). These procedures should be conducted at the investigational site.

After randomization, should a PVR urine volume level indicate a clinically meaningful elevation, the patient should be asked to void once again (allowing the patient sufficient time to void). The PVR urine volume will then be re-assessed. For patients who have a PVR urine volume measurement repeated, only the repeat value should be recorded in the eCRF.

Guidance on how to manage an elevated PVR urine volume, observed at any routine study visit or additional follow-up visit, is provided. In summary, post treatment PVR urine volume is divided into 3 categories:

1) < 200 mL
2) between ≥ 200 mL and < 350 mL
3) ≥ 350 mL

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

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

6.3.6.1 Post-void Residual Urine Volume < 200 mL

No protocol-required action needs to be taken. The patient continues to be reviewed as per the schedule of visits and procedures. CIC may be initiated only if the investigator deems it necessary for patient safety and will be recorded as a clinical decision.

6.3.6.2 Post-void Residual Urine Volume ≥ 200 mL and < 350 mL

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

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

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

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

        i. if the PVR urine volume 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

        ii. if the PVR urine volume is ≥ 350 mL then CIC should be initiated and managed as detailed below in the CIC section

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

            1. a central laboratory urinalysis and culture/sensitivity will be collected

2. if in the investigator's judgment CIC should be initiated, then CIC should be managed as detailed below in the CIC section

3. if CIC is not initiated and PVR urine volume continues to increase, the investigator will determine whether additional follow-up visits should occur

iv. if the PVR urine volume is decreasing or is unchanged then the patient will continue per the protocol schedule of visits and procedures.

6.3.6.3 Post-void Residual Urine Volume ≥ 350 mL

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

6.3.7 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; therefore, the Allergan Medical Safety Physician should be informed if an indwelling catheter is needed.

6.3.7.1 Initiation of Clean Intermittent Catheterization

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

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

The following will occur when initiating CIC (for elevated PVR urine volume as described above):

1) CIC is implemented and the patient should be instructed to perform CIC using sterile, single-use catheters (which will be provided to the patient)

2) an adverse event of urinary retention is recorded

3) central laboratory urine analysis and culture/sensitivity are performed as per routine requirements at each study visit excluding the clinic visit at Week 24.

4) the patient will be seen for a follow-up visit 1 week later where the PVR urine volume, associated symptoms, central laboratory urine analysis and culture/sensitivity will be reassessed. The investigator will determine whether the patient 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 patient record at each visit (ie, use/non-use). Start date of CIC should be documented, also.

6.3.7.2 Cessation of Clean Intermittent Catheterization

CIC should be discontinued when both of the following criteria are fulfilled:

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

These criteria can be met at any time after the start of CIC and do not need to be assessed only at a pre-scheduled visit. 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 must be documented and the reason given.

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

6.3.8 Adverse Events of Urinary Retention and Residual Urine Volume

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

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

6.3.9 Dipstick Reagent Strip Test (Urine Dipstick)

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

Urine dipstick tests are performed in conjunction with a central laboratory urine analysis and urine culture and sensitivity test.

Randomization/Day 1 Urine Dipstick Reagent Strip Test Results:

Patients with a positive dipstick test for nitrites or leukocyte esterase indicating a potential infection at Randomization/Day 1 must not receive any study treatment until results of the central laboratory urine analysis and urine culture/sensitivity test are obtained. If a bacterial infection is confirmed, the patient should be treated with antibiotics as determined by the investigator. The patient may return for a rescheduled Randomization/Day 1 visit (within 35 days of screening) and receive study treatment once a dipstick confirms a negative result for infection and all the 'Day of Treatment 1 Criteria' are fulfilled.

Treatment 2 Urine Dipstick Reagent Strip Test Results:

Patients with a positive dipstick test for nitrites or leukocyte esterase indicating a potential infection at the Treatment 2 visit, must not receive Treatment 2 until results from a central laboratory urinalysis and urine culture/sensitivity test are obtained. If a bacterial infection is confirmed, the patient should not receive Treatment 2, and the infection should be treated with antibiotics as determined by the investigator. The patient may return for Treatment 2 once a dipstick confirms a negative result for infection and all the 'Day of Treatment 2 Criteria' are fulfilled. Note: the qualification visit procedures do not need to be repeated (please refer to Section 5.10.2 Day of Treatment 2 Criteria).

6.3.10 Urinalysis, Culture and Sensitivity

Urinalysis will be performed at all study visits (excluding clinic visit at Week 24) by a central laboratory; a urine culture and sensitivity test will also be performed when central laboratory urine results are suggestive of a UTI (positive leukocyte esterase, nitrites, blood and/or microscopic sediments such as white blood cells [WBCs], red blood cells [RBCs] and/or bacteria).

Note: unscheduled central laboratory urinalysis and urine culture tests are performed if the PVR urine volume value at any visit is ≥ 200 mL (see Section 6.3.6 Full Bladder Volume and Post-void Residual Urine Volume).

6.3.10.1 Adverse Events of Urinary Tract Infection

Please refer to Section 9.1.2 for the study-specific definition of urinary tract infection adverse events.

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

6.3.11 Pregnancy Test

Urine pregnancy testing will be performed at the study site on women of childbearing potential at screening for Treatment 1 and the day of treatment visit for Treatment 1 and, if applicable, at the qualification visit for Treatment 2 and day of treatment visit for Treatment 2. A negative result is required prior to receiving study medication.

6.3.12 Screening Laboratory Tests

At screening, prior to Treatment 1, blood samples will be drawn from all patients for analysis of the following laboratory tests to be performed by the central laboratory: complete blood count, creatinine, and blood urea nitrogen. All male patients will undergo a prostate-specific antigen test also performed by the central laboratory.

[redacted]

6.3.14 Treatment Benefit Scale (TBS)

This single-item 4-point scale (Attachment 12.6) is used to assess the patient-reported benefit of treatment of OAB with respect to improvement or worsening of their condition (Colman et al, 2008).

6.4 Other Study Supplies

The following will be provided by Allergan:

- e-Diary with electronic patient bladder diaries

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

- prophylactic antibiotics required prior to study treatment
- sedation and anesthesia for use during study treatment
- sterile saline (or other appropriate sterile fluid) for bladder visualization during cystoscopic procedures and for reconstitution of study medication
- needles and syringes for reconstitution of study medication
- needles for cystoscopic injection
- sterile single-use catheters for CIC, if required
- flexible or rigid cystoscope with injection port
- ultrasound or bladder scan for PVR urine volume measurements
- refrigerator to store dry/reconstituted study medication at a temperature of 2 to 8ºC, monitored by a calibrated temperature recorder and temperature log
- internet connection (high-speed connection) for eCRF completion

6.5 Summary of Methods of Data Collection

An IWRS will be used to screen, randomize, terminate early, complete a study visit, complete the study participation, and manage study medication inventory. Data will be collected using eCRFs via a validated electronic data capture system (EDC). Source documents will be used and stored at the sites, and may include a patient's medical records, hospital charts, clinical charts, patient chart, copy of the EDC file, as well as the results of diagnostic tests such as laboratory tests and ultrasounds. The data will be transferred via secure server to Allergan.

7. Statistical Procedures

The statistical analysis will be conducted using all patients who have completed the study or exited the study prematurely. A detailed statistical analysis plan (SAP) will be finalized prior to the first database lock for interim analysis to provide further details regarding the definition of analysis variables and methodology to meet all study objectives.

7.1 Analysis Populations

Three populations will be used for the statistical analysis: Intent-to-treat (ITT), Modified intent-to-treat (mITT)and Safety.

ITT Population: The ITT Population will include all randomized patients. Demographics andbaseline characteristics will be analyzed using the ITT Population. Patients will be grouped and analyzed according to their randomization assignment, regardless of the actual treatment received.

mITT Population: The mITT Population will include all randomized subjects who had at least one efficacy assessment at baseline and a postbaseline visit. Efficacy variables will be analyzed using the mITT Population. Subjects will be grouped and analyzed according to their randomization treatment assignment, regardless of the actual treatment received.

Safety Population: The safety population will include all patients who receive the study drug (BOTOX or placebo). All safety variables will be analyzed using the Safety Population. Patients will be grouped and summarized according to the treatment they actually received.

7.2 Collection and Derivation of Primary and Secondary Efficacy Assessments

7.2.1 Primary Efficacy Variables

The primary efficacy endpoint is:

- Change from baseline in number of episodes of urinary incontinence at Week 12 as recorded by the patient in the 3-day bladder diary.

The following algorithms will be used for diary data conventions:

If there are no diary data (ie, none of the 3 diary days is a valid diary day), then the daily average frequency of urinary incontinence episodes will be considered as missing.

If a diary is completed for at least 1 day at any particular visit, then that patient's daily average frequency of urinary incontinence episodes in a 3-day period for that given visit will be estimated by using the daily average number of urinary incontinence episodes of the available days in the 3-day diary period.

A valid diary day is defined as a day in any of the three 24-hour periods with 2 or more urinary episodes of any type. For a valid diary day, if no incontinence episodes are recorded, the number of incontinence episodes on that day will be treated as zero. For an invalid diary day, both the number of incontinence episodes on that day will be treated as missing.

If the number of episodes of urinary incontinence at baseline is missing, it will be imputed using the median of all non-missing values regardless of treatment group at study baseline.

For each scheduled post-treatment visit, missing values for the primary efficacy variable will be imputed using the last observation carried forward (LOCF) approach. Additional details will be provided in the SAP.

7.2.2 Secondary Efficacy Variables

There are 5 secondary efficacy variables as follows:

- Proportion of patients who achieve 100% reduction in urinary incontinence episodes (complete continence) from baseline (ie, baseline prior to Treatment 1).
- Change from baseline in daily average number of micturition episodes.
- Change from baseline in daily average number of urgency episodes
- Change from baseline in daily average number of nocturia episodes.
- Proportion of patients who have a positive treatment response on the TBS (score of either 1 or 2, representing 'greatly improved' or 'improved', respectively).

The derivation of the first 3 secondary endpoints above, recorded from the 3-day bladder diary at each visit, will follow the same algorithm as for the primary efficacy endpoint described in Section 7.2.1.

7.3 Hypothesis and Methods of Analysis

Continuous variables will be summarized using mean, standard deviation, median, minimum value, and maximum value.

Categorical variables will be summarized using frequency counts and percentages.

Data will be listed in patient listings.

Statistical tests for all efficacy endpoints will be 2-sided at significance level of 0.05.

No adjustment for the multiplicity of the endpoints will be performed.

Additional details of the statistical analyses, methods, and data conventions will be described in the SAP.

7.3.1 Primary Efficacy Analyses

The primary efficacy endpoint is the change from baseline at Week 12 after study treatment in the daily average number of episodes of urinary incontinence in the 3-day bladder diary period.

The primary efficacy analyses will be based on the mITT Population, with imputation of missing values as described above in Section 7.2.1.

Let $\mu 1$, $\mu 2$ be the true mean change from baseline at Week 12 in the daily average number of episodes of urinary incontinence for BOTOX 100 U and placebo, respectively.

The hypothesis of the primary analysis will be formulated as

H0: $\mu 1 - \mu 2 = 0$ vs

HA: $\mu 1 - \mu 2 \neq 0$.

The hypothesis will be tested using an analysis of covariance (ANCOVA) model with treatment as a factor at 2 levels, and the number of UUI episodes reported at baseline (≤ 9 versus > 9 daily episodes, during the 3-day bladder diary at baseline) and baseline daily average number of episodes of incontinence as covariates. Least squares (LS) mean for each treatment and 95% confidence interval (CI) for $\mu 1 - \mu 2$ will be calculated.

In addition, baseline daily average number of urinary incontinence episodes and daily average number of urinary incontinence episodes at Week 12 within each treatment will be compared using a paired t-test.

In addition to the analysis provided above at Week 12, the same analysis will be applied to all other scheduled visits.

7.3.2 Secondary Efficacy Analyses

The 5 secondary endpoints are listed in Section 7.2.2.

The analysis of all secondary endpoints will be based on the mITT Population.

The first and the last secondary endpoints on the list are categorical variables, and they will be analyzed using a Cochran Mantel-Haenszel (CMH) test with the number of UUI episodes reported at baseline (≤ 9 versus > 9 daily episodes, during the 3-day bladder diary at baseline) as another categorical factor at each scheduled visit. Point estimate and the 95% CI for the odds ratio (BOTOX 100 U/placebo) will be calculated.

The second to the fourth secondary endpoints on the list are continuous variables. Each of the 3 continuous endpoints will be analyzed at each scheduled visit using an ANCOVA model with treatment as a factor and baseline value corresponding to the given endpoint and the number of UUI episodes reported at baseline (≤ 9 versus > 9 daily episodes, during the 3-day bladder diary at baseline) as covariates. A 95% CI for the LS mean difference of a given endpoint between the 2 treatments will be calculated. A paired t-test will be performed to compare the baseline value to a post-treatment value at each visit for each endpoint.

between the 2 treatments will be constructed. A paired t-test will be performed for the comparison between baseline and a post-treatment value at each visit for each endpoint.

The categorical endpoints will be analyzed using a CMH test with the number of UUI episodes reported at baseline (≤ 9 versus > 9 daily episodes, during the 3-day bladder diary at baseline) as another categorical factor at each visit. Point estimate and 95% CI for the odds ratio will be calculated for each endpoint at each visit.

The time-to-first-event endpoint will be analyzed using the Kaplan-Meier procedure for median time-to-request of re-treatment event by days (and weeks). Between-group comparisons of the 2 treatments will be performed using the log-rank test. A 95% CI for the median time-to-request of re-treatment for each treatment will be calculated.

7.3.4 Safety Analyses

All safety analyses will be conducted on the safety population.

Descriptive statistics will be used to summarize safety endpoints which include adverse events, clinical laboratory (urine analysis), vital signs, PVR urine volume, physical examination, CIC use, concurrent procedures, and concomitant medications.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 19.0 or later). Adverse events will be summarized by primary system organ class and preferred term for each treatment. This summary will include all treatment-emergent adverse events (TEAEs) recorded from first dose of study treatment up to the post-treatment follow-up. Tables of fatal adverse events, SAEs, and adverse events leading to study discontinuation will be summarized by treatment. TEAEs by severity and relationship to study drug will be summarized by treatment.

Parameters for urine analysis will be summarized descriptively by treatment at each visit during the study. Shift tables will be provided for selected laboratory parameters.

Vital signs and PVR urine volume, will be summarized descriptively for each treatment by visit. Change from baseline in PVR urine volume (continuous variable) will also be performed.

Concurrent procedures and concomitant medications will be summarized descriptively for each treatment.

[redacted]

7.5 Sample Size Calculation

The assumptions used for the sample size calculation are from the Phase III pivotal studies (191622-095 and 191622-520) results.

Assuming a mean and standard deviation of change from baseline at Week 12 in the number of urinary incontinence episodes are -2.8 (±3.45) and -0.95 (±2.9) for BOTOX 100 U and placebo, respectively, this study requires 102 patients with a 2:1 ratio (68 BOTOX patients and 34 placebo patients) to provide 80% power for detecting a significant difference of the primary efficacy endpoint (change from baseline in number of urinary incontinence episodes at Week 12) at a significance level (alpha) of 5% using a 2-sided z-test at the end-of-study double-blind analysis.

With a 10% dropout rate (based on the pooled Phase III pivotal studies), the sample size required for the patients to be randomized in the study is approximatly 114.

PASS 2008 sample size software was used to calculate the sample sizes.

7.6 Primary Analysis

A primary analysis will occur when all patients have completed 12 weeks following Treatment 1 (double-blind period) or early terminated. Only tables will be produced (no patient listings will be produced), thus maintaining patient and site/investigator treatment blinding. The primary analysis (topline data) will be a subset of the final analyses performed for the final CSR. Analyses included in the primary analysis will be flagged in the SAP list of table, figure, and listing mocks.

The main purpose of the primary analysis is for presentation of the key data as soon as possible at an international urological or urogynecological conference to ensure dissemination of results in a timely manner. The topline primary analysis data will include key efficacy and safety analysis from the first 12 weeks after treatment 1 (double-blind data).

For the purpose of the primary analysis, statistics and programming staff from the vendor CRO, will have blinded and unblinded teams set up for the analysis, per details contained in the SAP and/or other documentation listing those who will be unblinded. Unblinded statistical team will work in a restricted secure study location.

Only Allergan study team members and corresponding co-authors will receive the topline primary analysis data (no analysis datasets and listings will be distributed, therefore the Allergan team and co-authors will not be unblinded to patient level data). Those who will be unblinded in Allergan will be listed in an other document. No CSR will be authored following the primary analysis.

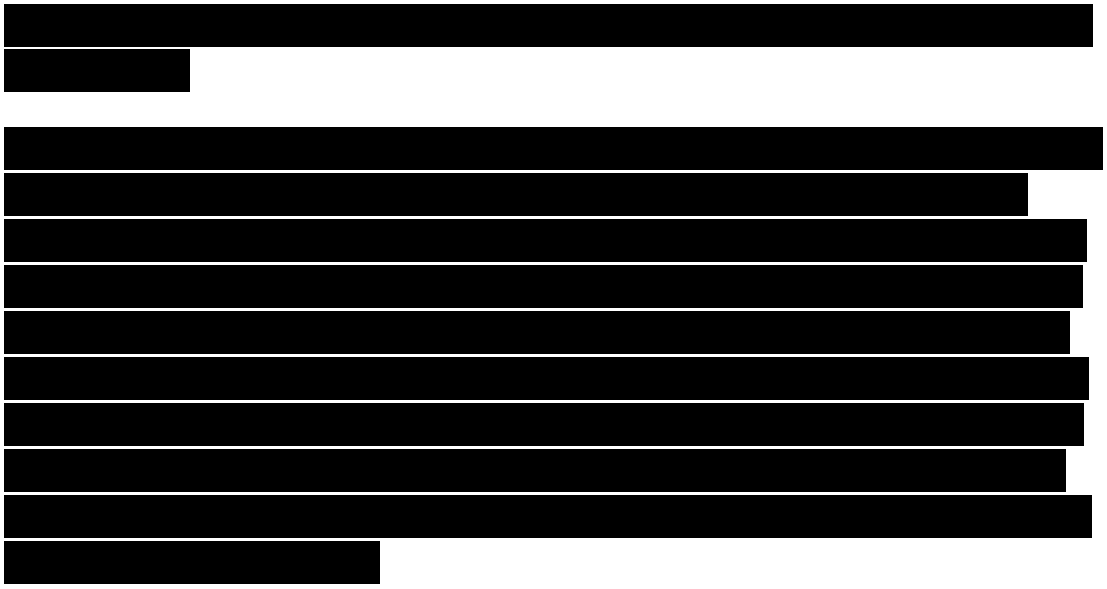
Full unblinding will occur following the final database lock at the end of the study, for the final CSR.

8. Study Visit Schedule and Procedures

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

The visit schedule is described below.

Also, the occurrence of adverse events and SAEs at any time after informed consent through the post-treatment exit visit will be monitored and recorded. Use of concomitant medications will be recorded during the screening period, treatment and post-treatment follow-up through the exit visit.



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Unscheduled visits will be performed if safety concerns arise, at the discretion of the investigator, as well as for qualification for Treatment 2 in the case of a patient's request for retreatment occurring outside the prescheduled visits. Additional examinations may be performed as necessary to ensure the safety and well being of patients during the study. Additional unscheduled visits will occur if a patient has a post-treatment PVR urine volume of ≥ 200 mL (for additional details see Section 6.3.6 Full Bladder Volume and Post-void Residual Urine Volume).

8.1 Subject Entry Procedures

8.1.1 Overview of Entry Procedures

Prospective subjects as defined by the criteria in Sections 4.3 and 4.4 (inclusion/exclusion criteria) will be considered for entry into this study.

8.1.2 Informed Consent and Subject Privacy

The study will be discussed with the patient, and a patient wishing to participate must give informed consent prior to any study-related procedures or change in treatment. The patient must also give authorization in accordance with any local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

Each patient that provides informed consent will be assigned a patient number that will be used on patient documentation throughout the study.

8.2 Washout Intervals

Patients who are currently receiving pharmacologic therapy to treat the symptoms of OAB and who have consented to participate in the study must stop the therapy at least 7 days prior to the start of the screening period procedures.

8.3 Procedures for Patient Rescreening

A patient who is screen-failed due to misunderstanding how to input data into the e-Diary may be considered for rescreening if the investigator determines that the patient is otherwise qualified to participate in the study and meets all other Inclusion/Exclusion criteria. The investigator may request permission for rescreening of the patient from the Allergan Medical Director for the study, who will make a decision on a case-by-case basis.

A patient confirmed by Allergan Medical Director to be eligible for rescreening will first be screen failed. The patient will be reconsented and receive a new study identification number and a new e-Diary for rescreening. The patient will retain the new number during successful screening and for the remainder of the study. All original data will be retained and available in the EDC and e-Diary databases; but only the data from their second screening period will be included in data analysis. An accounting indicating both study numbers for patients who rescreened will be included in the Clinical Study Report (CSR).

8.4 Procedures for Final Study Entry

Final study eligibility will be determined at the Randomization/Day 1 visit to confirm that patient bladder diary records support protocol requirements for urinary incontinence. In addition, prior to randomization, the investigator should confirm that the Day of Treatment 1 Criteria have been fulfilled (Section 5.9.1). Patients should continue to meet other inclusion and exclusion criteria as specified in Sections 4.3 and 4.4 of the protocol.

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

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

8.5 Visits and Associated Procedures

For a summary of the procedures to be performed, see Table 1 (Schedule of Visits and Procedures). A description of individual procedures is provided in Section 6.3. The total number of clinic visits and study duration for each patient will depend on the number and timing of treatments received by the patient. Evaluations should be performed by the same

evaluator throughout the study whenever possible. During the study, every effort should be made to perform the study procedures as indicated in Table 1.

Instructions for the Subjects

Patients will be instructed on the following:

- to discontinue any anticholinergic (if applicable), as described in Section 8.2 Washout Intervals
- to discontinue medications with anticoagulative effects a minimum of 3 days (or longer according to the clinical judgment of the investigator) and antihistamines for 2 days prior to any study treatment, as described in Section 4.5.1 Permissible Medications/Treatments, and Section 4.5.2 Prohibited Medications/Treatments
- to take antibiotics as described in Section 5.9.2 Prophylactic Antibiotics
- bladder diary completion (Section 6.3.4 Bladder Diary), including the appropriate procedure for volume voided collection (Section 6.3.5 Total Volume Voided)
- health outcomes questionnaire completion (I-QOL and TBS), as described in Section 12.4 Instructions for Completion of Questionnaires
- to contact the study site (or have a family member or friend contact the study site) to report any hospitalizations
- to maintain the dose of any concurrent medication. If there are changes to medications, dosage, or frequency, the changes should be reported to the investigator at the next study visit.
- that any use of CIC or indwelling catheter (the latter of which is prohibited) should be communicated immediately to the investigator
- to call the study site if they are experiencing any difficulties following study procedures
- to call the study site as soon as possible in order to reschedule, if the patient cannot make their next scheduled study visit

8.6 Unscheduled Visits

Unscheduled visits can be performed if safety concerns arise and at the discretion of the investigator. Additional examinations may be performed as necessary to ensure the safety and well being of patients during the study. eCRFs will be completed for each unscheduled

visit. See Sections 6.3.6 and 6.3.7 for guidelines on procedures to be performed for unscheduled visits related to raised PVR urine volume or CIC usage.

8.7 Compliance with Protocol

Participating patients must be able to adhere to the diary completion and testing parameters as described in this protocol.

Data will be recorded on the appropriate eCRF supported by appropriate source documentation. At each clinic visit and at the phone contact at Week 1, patients should be asked if any concomitant medications have been used or if they have undergone any concurrent procedures (non-study procedures), as well as their compliance with the protocol since the previous clinic visit/phone conversation. If medications were taken for UTI, the UTI medication name should be recorded separately from other concomitant medications, in the designated field in the CRF.

8.8 Early Discontinuation of Subjects

Patients may voluntarily withdraw from the study at any time. The early patient discontinuation from the study and the reason for discontinuation will be clearly documented on the appropriate eCRF. If a patient exits the study prior to study completion (ie, Treatment 1 plus a 30-week follow-up period, or if a second treatment is received at least 12 weeks post treatment follow-up), all exit visit assessments should be performed at the time of exit. Any adverse event that is marked 'ongoing' at the exit visit must be followed-up as appropriate, eg, until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up.

8.9 Withdrawal Criteria

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

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

- patient develops (or has an exacerbation of) any medical condition that, in the opinion of the investigator, would put the patient at an unacceptable medical risk or compromises the patient's ability to participate in the study
- patient is diagnosed with new or recurrent malignancies, except basal cell carcinoma

- patient becomes pregnant (see Section 4.5.1.1 Definition of Females of (Non-) Childbearing Potential and/or Acceptable Contraceptive Methods)
- patient is unwilling or unable to continue to comply with study procedures.

Where possible, the decision to withdraw a patient from the study or study treatment should be discussed with Allergan. A patient who is withdrawn prematurely from the study should complete assessments as described in Section 8.8.

8.10 Study Termination

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

9. Adverse Events

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

9.1 Definitions

9.1.1 Adverse Event

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

9.1.2 Study-specific Definitions for Particular Adverse Events

Definition of Adverse Event of Urinary Retention:

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

- Patient has a PVR urine volume of ≥ 350 mL (regardless of symptoms), OR
- Patient has a PVR urine volume ≥ 200 mL and < 350 mL and the patient 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 urine volume is clinically significant but does not fulfill the above definition for urinary retention.

Definition of Adverse Event of Urinary Tract Infection:

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

- A positive urine culture result with a bacteriuria count of > 105 colony forming units/mL
- Leukocyturia of > 5/high-power field

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

9.1.3 Serious Adverse Event

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

Allergan considers all cancer adverse events as SAEs. In addition, Allergan considers any abortion (spontaneous or nonspontaneous) as an SAE.

9.1.4 Severity

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

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

9.1.5 Relationship to Study Drug or Study Procedure

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

9.2 Procedures for Reporting Adverse Events

Any adverse event must be recorded in site source documents from the time of informed consent through study exit. Any adverse event occurring after subject randomization through study exit must also be recorded on the appropriate eCRF.

All adverse events that are drug-related and unexpected (not listed as treatment-related in the current Package Insert) must be reported to Allergan Pharmacovigilance, the governing Institutional Review Board (IRB) as required by the IRB, local regulations, the governing health authorities. Any event that is 'ongoing' at the exit visit must be followed-up as appropriate, eg, until resolution, stabilization, until the event is otherwise explained, or the participant is considered lost to follow-up.

9.3 Procedures for Reporting a Serious Adverse Event

Any serious adverse event (SAE) occurring from the time of randomization up to study exit must be immediately reported to an Allergan representative listed on the Allergan personnel page and recorded on the SAE Fax Form within 24 hours of awareness. Patients with significant or drug-related SAE's as determined by the investigator must be followed up and the outcomes reported to Allergan. The investigator must supply the sponsor and the IRB with any additional requested information (eg, autopsy reports and terminal medical reports). Pre-scheduled hospitalizations (ie, pre-scheduled surgery) are not considered an SAE and should not be reported as such. Note: Generally, awareness of adverse events (S/AE's) after study exit is not reportable, unless determined significant by the investigator on a case-by-case basis. Such events should be reported to Allergan Pharmacovigilance, but are not required to be captured in the CRF.

In the event of an SAE, the investigator must:

1. Notify Allergan immediately (within 24 hours) by fax or e-mail using the SAE reporting forms (for SAE fax number and e-mail address, see page 1 of the protocol). Emergency phone numbers and relevant Allergan personnel contacts are also on the front page of protocol.
2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.
3. Provide Allergan with a complete, written case history (adverse event report form) which includes a statement as to whether the event was or was not related to the use of the investigational drug.
4. Promptly inform the governing IRB of the SAE as required by the IRB, local regulations, and the governing health authorities.

9.4 Procedure for Reporting Pregnancy

If a female of childbearing potential becomes pregnant during the study, the investigator will notify Allergan immediately after the pregnancy is confirmed (using the Pregnancy Communication Form, Pre-Delivery) and the patient will be exited from the study after appropriate safety follow-up, which must be a minimum of 12 weeks since last study treatment. The investigator will (1) notify the patient's physician that the patient may have been treated with BOTOX, and (2) follow the progress of the pregnancy. The investigator or designee should document the outcome of the pregnancy and provide a copy of the documentation to Allergan (using the Pregnancy Communication Form, Post-Delivery Information).

9.5 Procedures for Unmasking of Study Medication

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

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

10. Administrative Items

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

10.1 Protection of Human Subjects

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

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

10.1.2 Compliance with IRB or IEC Regulations

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

10.1.3 Compliance with Good Clinical Practice

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

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

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

10.2 Changes to the Protocol

The investigator must not implement any deviation from or changes of the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment, except where necessary to eliminate immediate hazards

to study subjects, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers).

10.3 Patient Confidentiality

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

10.3.1 Patient Privacy

Written authorization, and other documentation in accordance with the relevant country and local privacy requirements (where applicable) is to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (eg, the Health Insurance Portability and Accountability Act Standards for Privacy of Individually Identifiable Health Information ("HIPAA").

In accordance with HIPAA requirements, additional purposes of this study include the following:

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

10.4 Documentation

10.4.1 Source Documents

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

The following information should be entered into the patient's medical record:

- patient's name
- patient's contact information

- date that the patient entered the study and medication kit number
- study title and/or the protocol number of the study and the name of Allergan
- a statement that informed consent was obtained (including the date). A statement that written authorization (US sites only) or other country and local patient privacy required documentation for this study has been obtained (including the date)
- dates of all patient visits
- medical and surgical history
- previous anticholinergic use and reason for discontinuation
- all concurrent medications. (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications should be recorded).
- dates of study treatment administration
- date(s) of patient request for retreatment and reason
- date of qualification for retreatment
- occurrence and status of any adverse events (including any procedure-related adverse events)
- post-void residual urine volumes
- physical examination findings, including height and weight
- vital signs
- date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation
- results of laboratory tests performed by the site (eg, results of urine pregnancy tests, urine dipstick)
- results, if applicable, of any procedures performed to confirm eligibility criteria (eg, follow-up on abnormal urine cytology findings, etc.)
- reason, if applicable, de novo CIC not discontinued in accordance with criteria stated in Section 6.3.6.2 Post-void Residual Urine Volume ≥ 200 mL and < 350 mL

Patient's response to the following questionnaire/assessments entered directly onto the appropriate electronic form will be considered source data:

- I-QOL questionnaire
- TBS questionnaire
- Patient bladder diary

In addition, study drug accountability and reconstitution records will be retained as source documentation.

10.4.2 Electronic Case Report Form Completion

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

10.4.3 Study Summary

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

10.4.4 Retention of Documentation

All study-related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of eCRFs should be maintained on file in electronic format. Also, as a backup, the electronic files are to be maintained on a removable storage device in a secure location with restricted access maintain confidentiality of patients' medical records and personal information.

For countries falling within the scope of the ICH guidelines, the sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

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

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

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

10.5.1 Labeling/Packaging

Investigational material for injection will be packaged and labeled in identically appearing vials. The study treatment will be identified as an investigational compound on the unit label with the study number and a kit number.

10.5.2 Clinical Supply Inventory

The investigator must keep an accurate accounting of the number of investigational units (vials) received from Allergan and administered at the completion of the study. A detailed inventory must be completed for the study medication.

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

All clinical study medications/treatments and/or supplies will be returned to Allergan or Allergan designee for destruction. Study medication remaining in the dosing syringes will be disposed of per local site practice.

10.6 Monitoring by the Sponsor

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

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

10.7 Handling of Biological Specimens

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

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

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

10.8 Publications

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

10.9 Coordinating Investigator

A signatory Coordinating Investigator will be designated prior to the writing of the Clinical Study Report.

11. References

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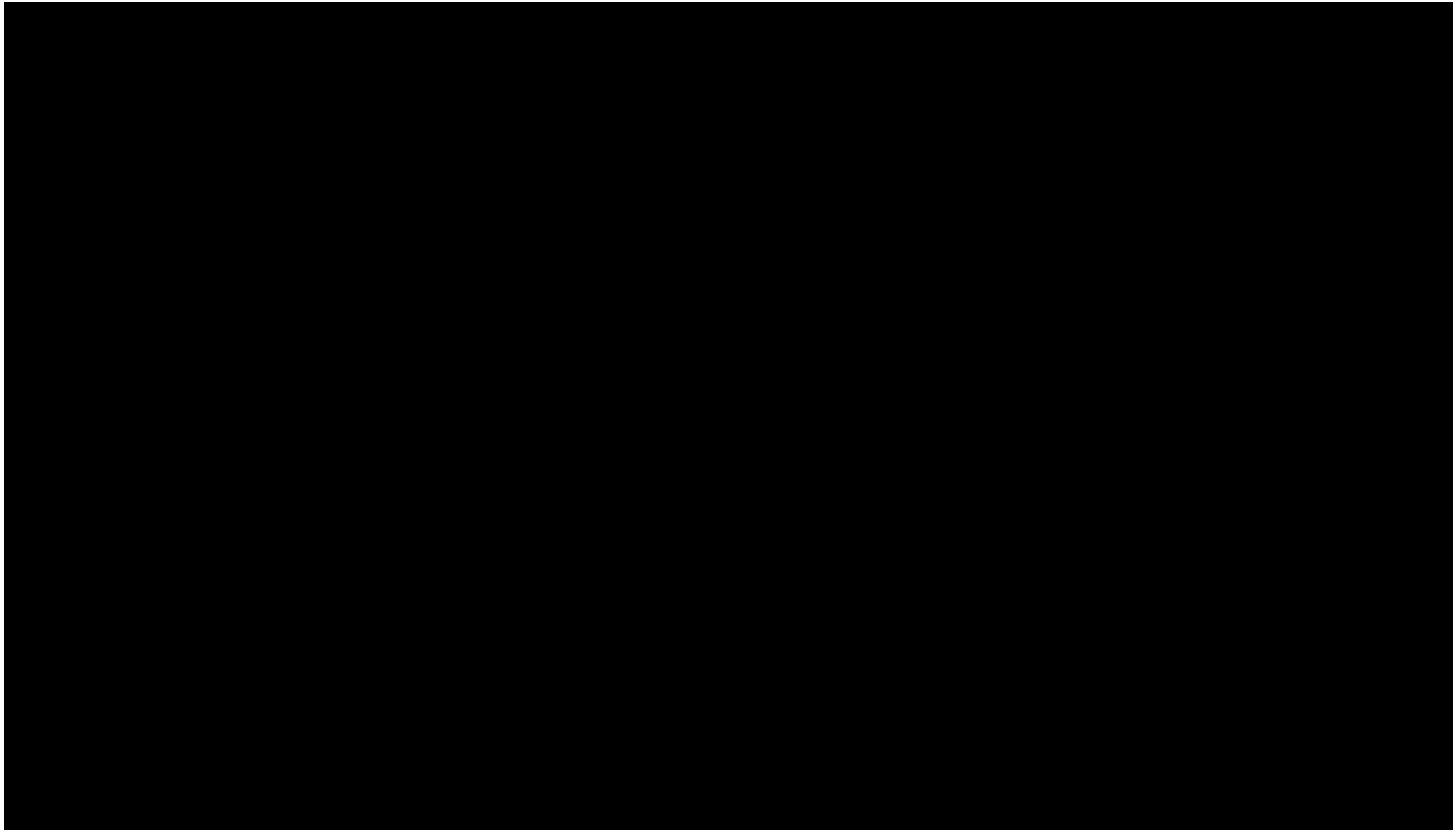
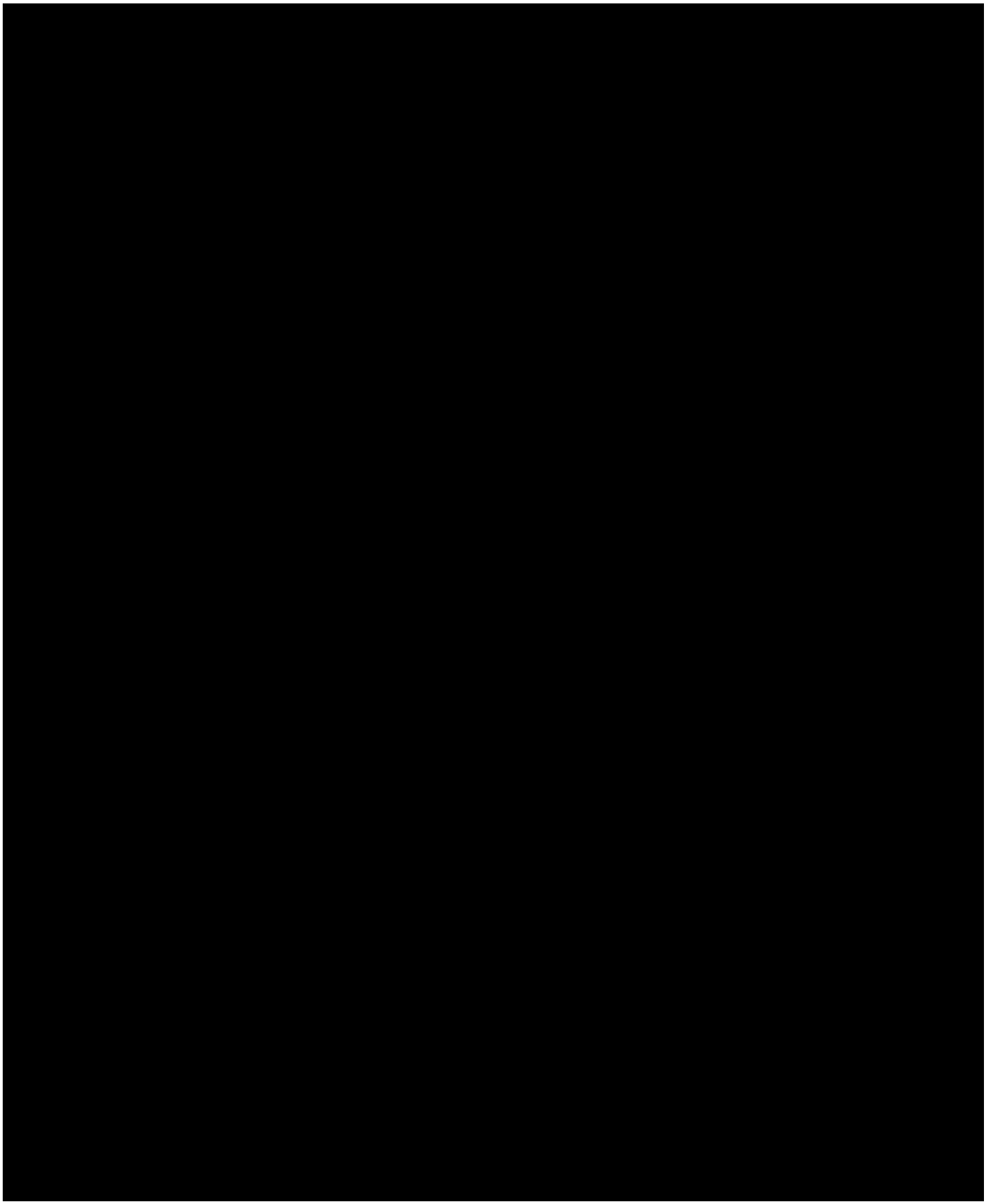
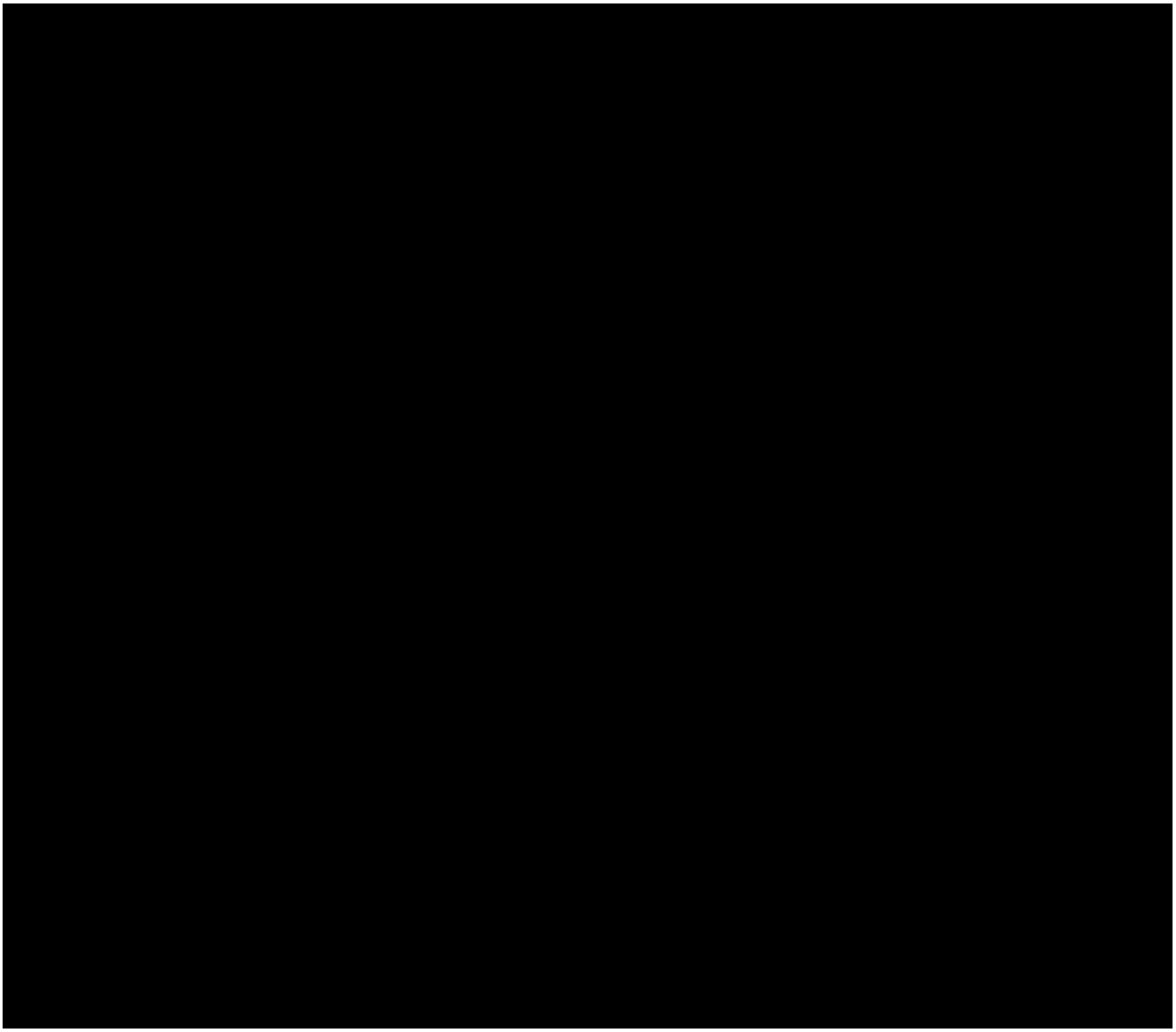
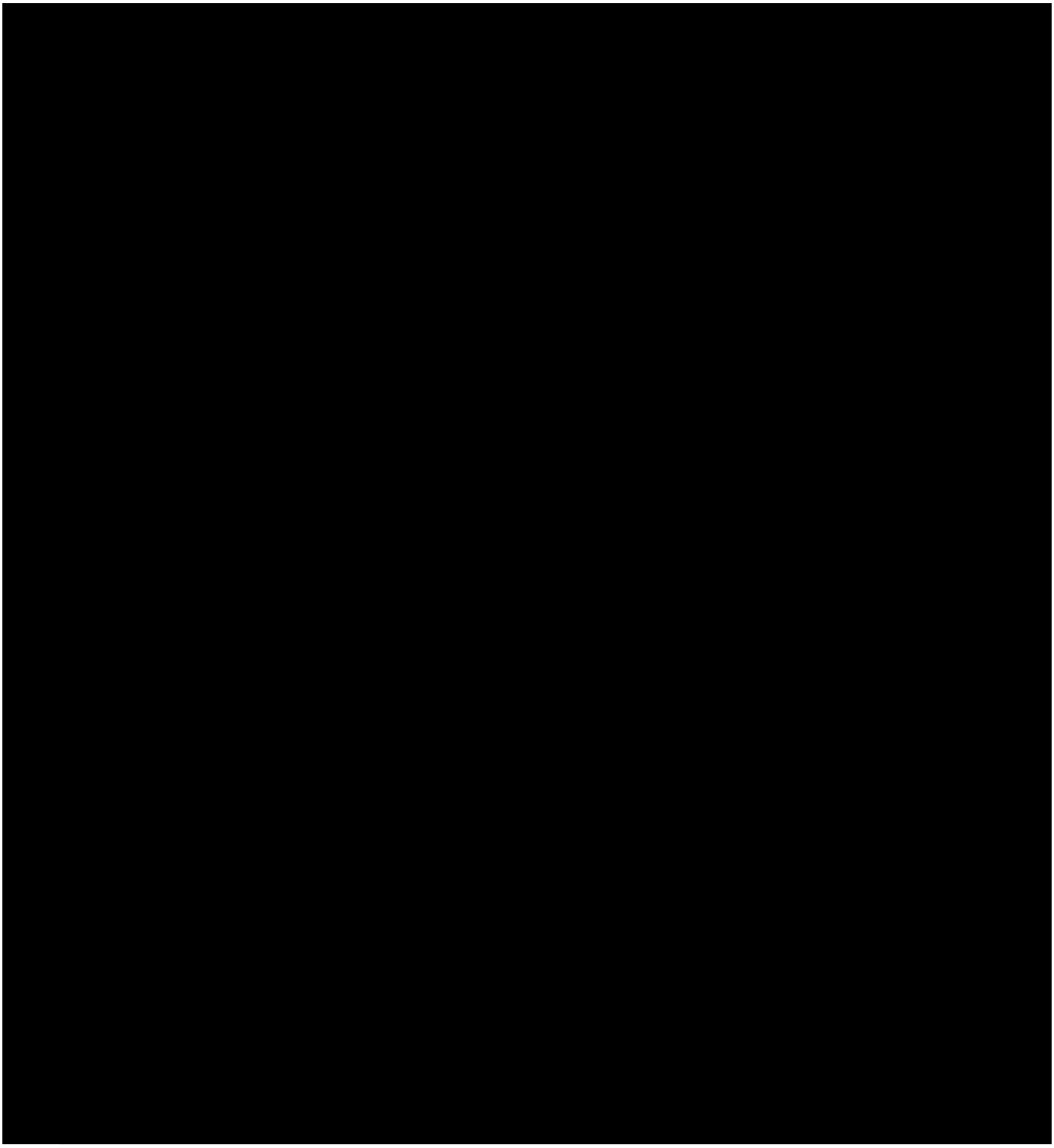
12.1 Preparation of Study Medication

Study medication vials will be reconstituted based on the following table:

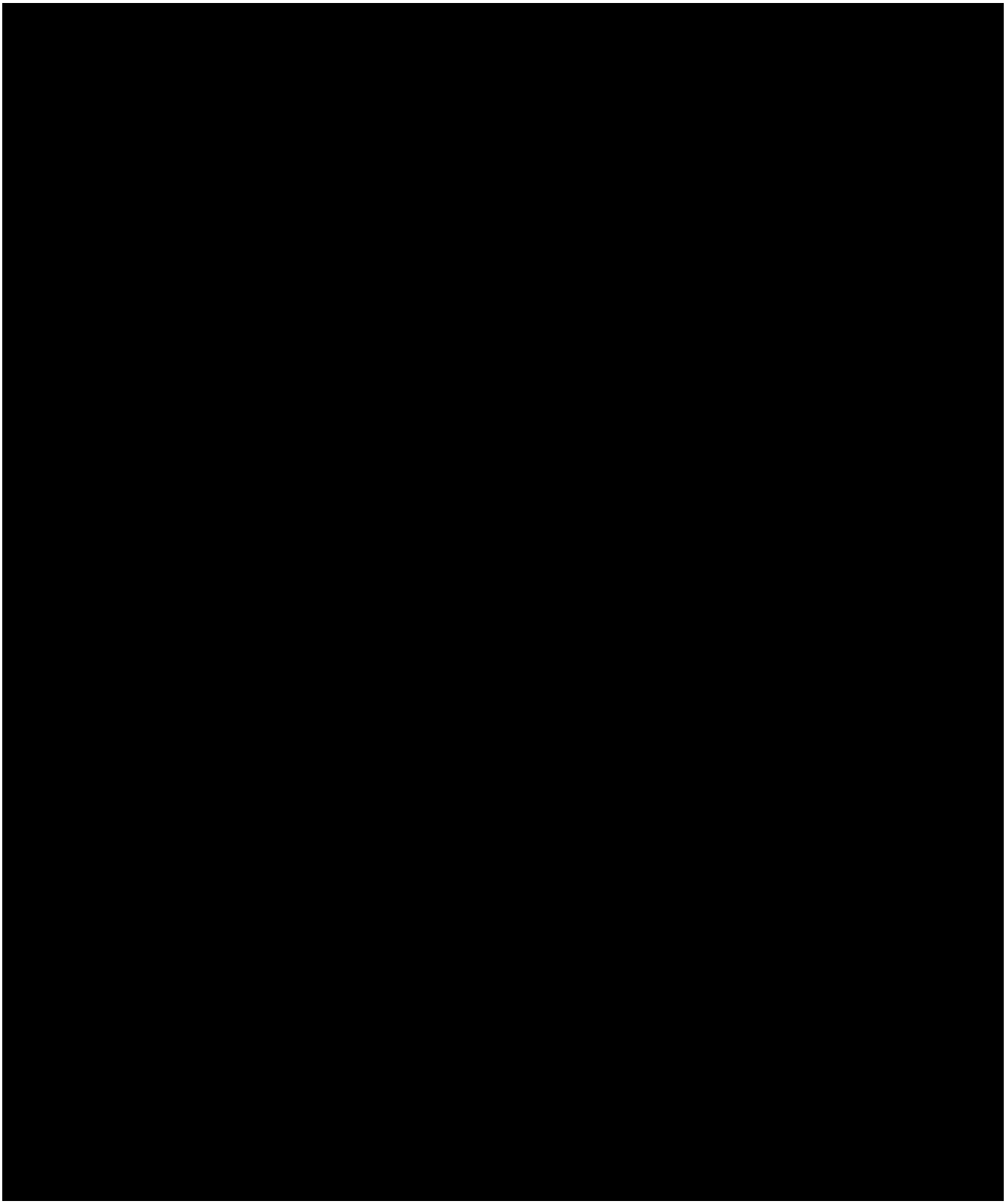


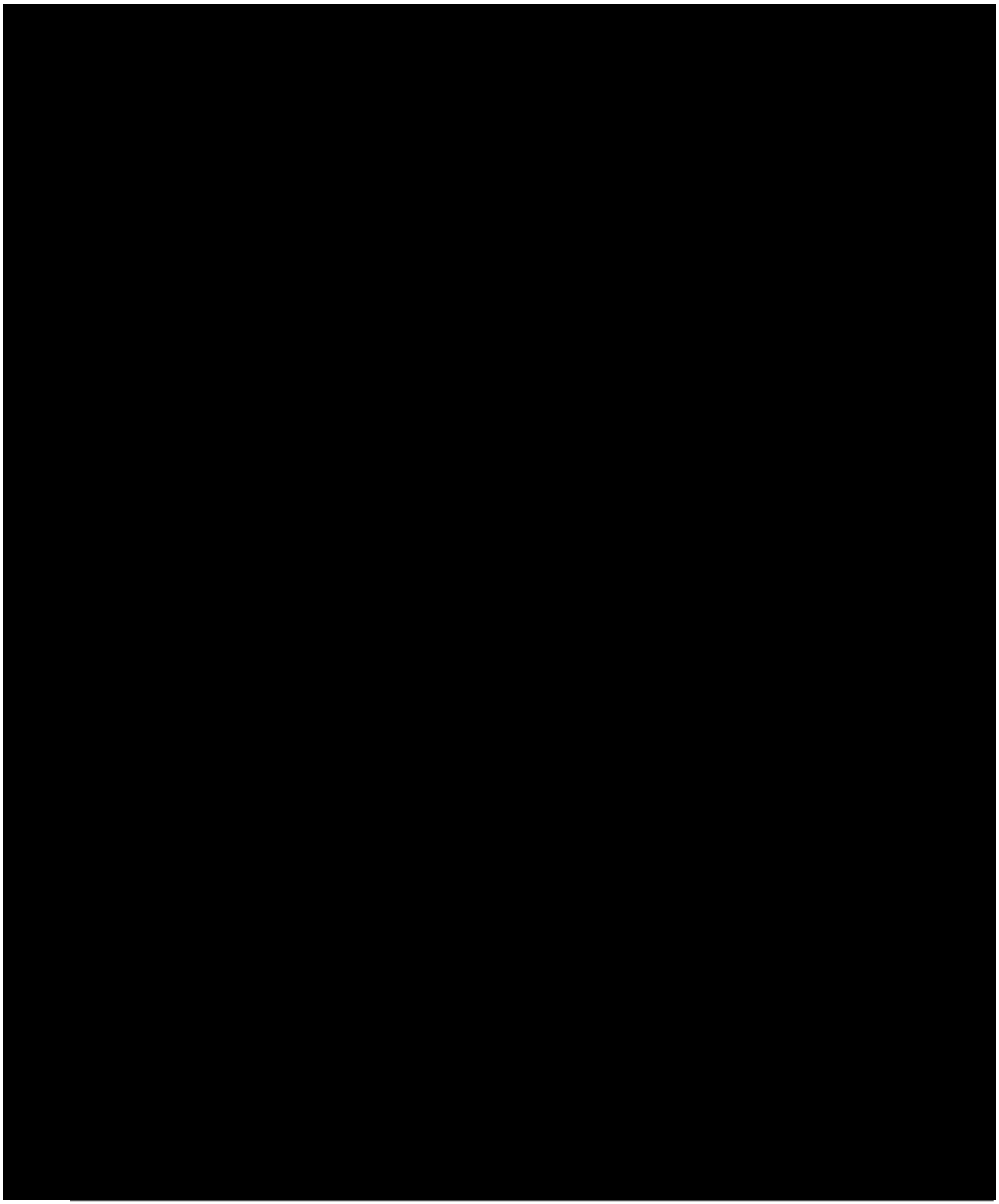


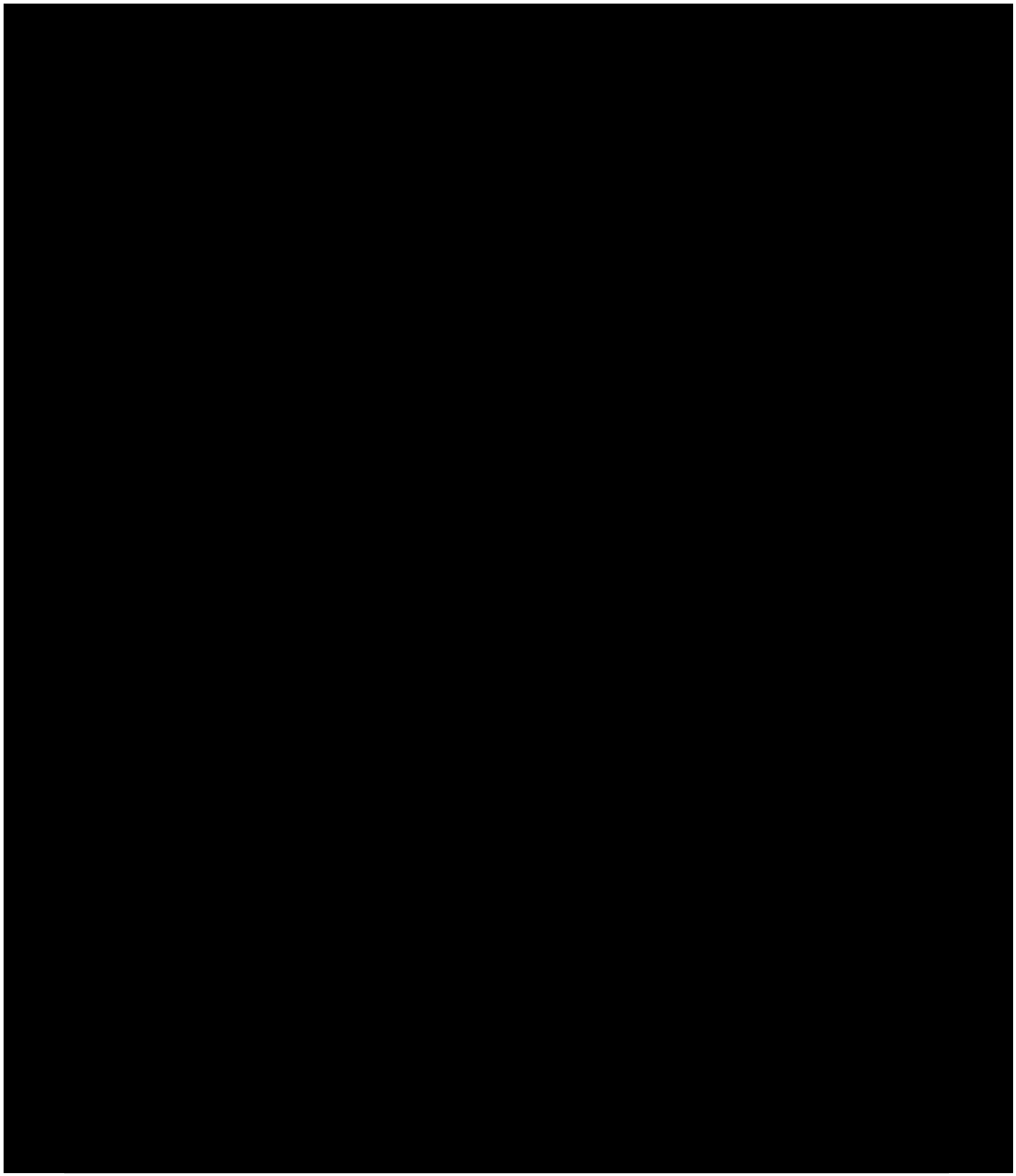


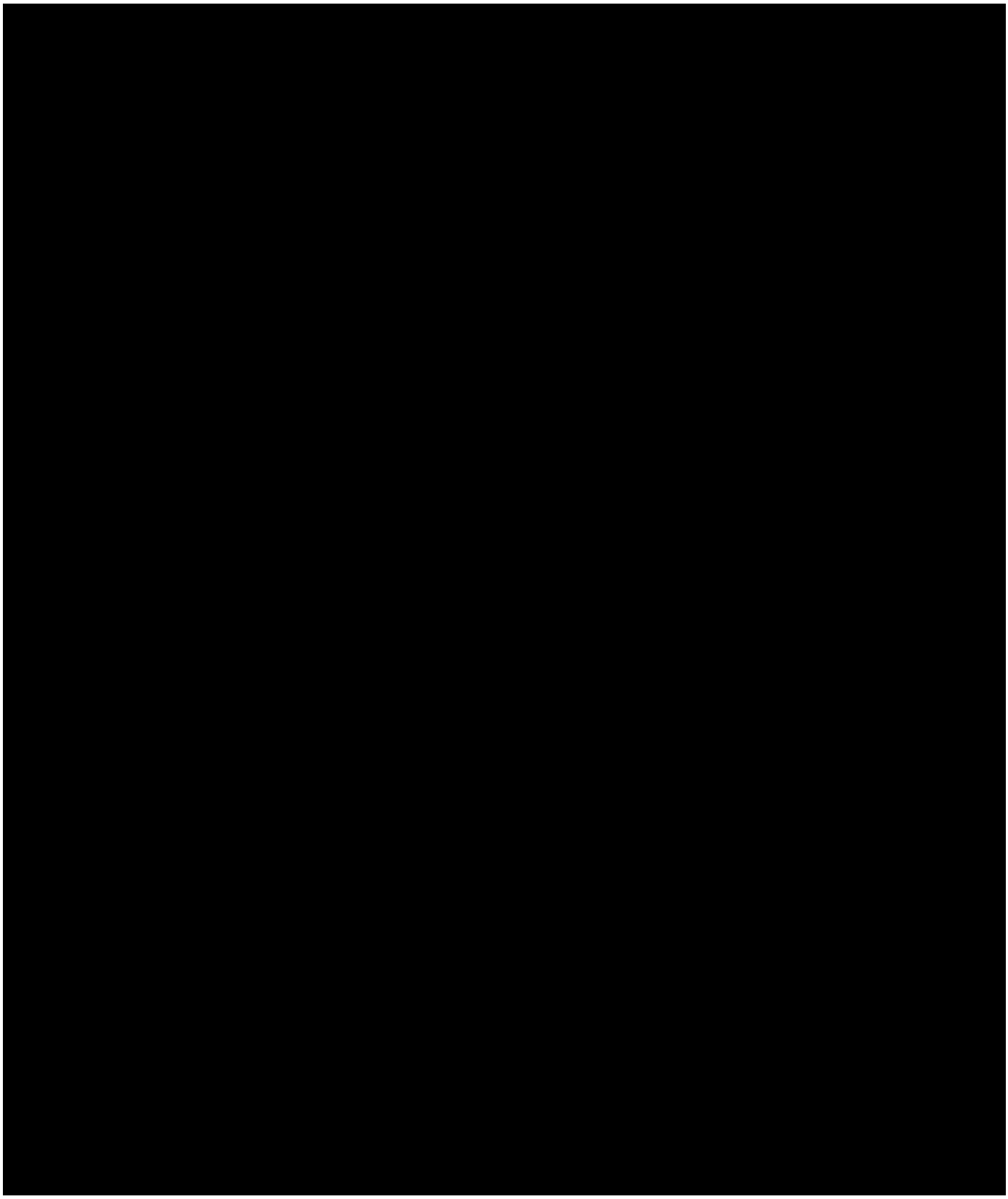


English (US) version









English (US) version

I-QOL

12.6 Treatment Benefit Scale (TBS)

Please complete the following question by considering your current condition urinary problems, urinary incontinence) compared to your conditon **before you received any study treatment in this trial**.

My condition has

< greatly improved

< improved

< not changed

< worsened

during treatment.

12.7 Package Insert

The US package insert will be supplied to investigators.

12.8 Glossary of Abbreviations

Term/Abbreviation	Definition
ANCOVA	analysis of covariance
BOTOX	Botulinum Toxin Type A Purified Neurotoxin Complex (US adopted name onabotulinumtoxinA), referred to as BOTOX
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CIC	clean intermittent catheterization
CFR	Code of Federal Regulations
CMH	Cochran Mantel-Haenszel
eCRF	electronic case report form
EDC	electronic data capture
e-Diary	electronic diary to collect data for clinical outcome assessment (e-COA)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEENT	head, eyes, ears, nose, throat
HIPAA	Health Insurance Portability and Accountability Act
HRQOL	health-related quality of life
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
I-QOL Questionnaire	Incontinence Quality of Life Questionnaire
IRB	Institutional Review Board
ITT	intent to treat
IWRS	interactive web response system
KHQ	King's Health Questionnaire
LD_{50}	lethal dose to 50% of animals
LOCF	last observation carried forward
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat
NSAID	nonsteroidal anti-inflammatory drug
OAB	overactive bladder
PSA	prostate-specific antigen
PTNS	peripheral tibial nerve stimulation
PVR	post-void residual
QOL	quality of life
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan

Term/Abbreviation	Definition
TBS	Treatment Benefit Scale
TEAE	treatment-emergent adverse event
US	United States
UTI	urinary tract infection
UUI	urgency urinary incontinence
WBC	white blood cell

12.9 Protocol Amendment

Summary of Changes with Amendment 1

Change Made	Section
Adminstrative changes	Title page
	4.3
	8.9
	10.3.1
Increased the estimated duration of enrollment.	3
Clarified language around the use of antihistimines prior to treatment	4.5.1
	8.5
Clarified no prior washout required for muscle relaxants (beyond not taking the medication on the day of treatment).	4.5.2
Clarified that assessment of urinalysis and urine culture results from Screening are to be used to determine eligibility for Treatment 1.	Synopisis
	5.9.1
Clarified that Symptoms and history of bladder stones or bladder malignancies should be part of clinical assessment to determine criteria for Treatment 1.	Synopsis
	5.9.1
Clarified that prophylactic antibiotics may be given 1-3 days prior to treatment.	Synopsis
	Schedule of visits and proceedures footnotes
	5.9.1
	5.9.2
	8
Correction to incorrect wording to clarify that antibiotics to continue for 1 to 3 days post treatment	Schedule of visits and proceedures footnotes
Clarified that assessment for urinary tract infection prior to Treatment 2, may include results of urine culture and sensitivity from Qualification.	5.10.2
Clarified that leukocyte esterase is a test for white blood cell counts (WBC).	Synopsis
	5.9.1
	5.10.2

Change Made	Section
Primary Analysis added and described in detail (this section was previously termed interim analysis, previously planned interim analysis details removed)	7.6 5.9.1 5.10.2
Added and defined the circumstances and procedures for rescreening patients where there was a misunderstaning in completing the e-Diary.	8.3
Clarified that all adverse events will be documented at study sites from the time of consent, whether or not a patient has been treated. Only adverse events occurring after a patient has been randomized will be entered on the appropriate eCRF pages.	Schedule of visits and proceedures footnotes
Provided additional clarification on AE/SAE/Pregnancy reporting.	9.1.1 9.2 9.3 9.4
Clarified that no study procedures, including completion of study questionnaires or diaries will take place prior to patient providing informed consent to participate in the study.	12.4
Clarified that the term, “first morning void,” for the purposes of the study means the first void after a patient gets up in the morning with the intent to stay awake.	12.3
Deleted references to IVRS (interactive voice response system) as the study uses an interactive web response system (IWRS).	Synopsis 3 5.4 5.5 6.5 9.5 12.1 12.8
Inserted language that all study materials will be created and supplied in English language. There are no plans to translate any study materials into other languages.	Synopsis
Changed the randomization target from 240 subjects to approximately 114 (68 Botox patients and 34 Placebo patients; based on sample size calculation of primary endpoint). With an estimated drop-out rate of 10%, approximatly114 patients will be randomized.	Synopsis 4.1 7.5

Change Made	Section
Included language that subjects be aware they should not change their life habits around fluid consumption and micturition while participating in the study.	Synopsis
Added wording to clarify that the bladder diary was collected as an eDiary and replaced previous term of personal digital assistant (PDA)	Synopsis 6.3.4 6.4 8 12.4 12.8
Removed wording stating that Proportion of patients who achieve 100% reduction in urinary incontinence episodes is a key secondary measure	Synopsis 6.1.2 7.2.2
Clarified that where the independent review board (IRB) does not agree to permitting the temporary discontinuation of anticoagulant/antiplatelet medications, then patients using these medications will not be enrolled.	4.5.1
Clarified that 2-sided statistical test at a significance of 0.05 will be used for primary endpoint	7.3
Clarified how the hypothesis of the primary analysis has been formulated	7.3.1
PVR urine volume no longer listed as efficacy measure, however remains as a safety measure and will continue to have a change from baseline analysis performed	Synopsis 6.1.3 7.2.3 7.3.4
Modified Intent-To-Treat (mITT) analysis added to include all randomized subjects who have at one efficacy assessment at baseline and a postbaseline visit. Efficacy variables will be analyzed using the mITT Population.	Synopsis 7.1 7.3.1 7.3.2 7.3.3