# Intraprostatic Injection of Botulinum Toxin for the Management of Benign Prostatic Hyperplasia: A Randomized Phase II Trial

# PROTOCOL

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Developed and Conducted by the
MIST Study Group

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## 1 Introduction and Objectives

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) has sponsored a collaborative agreement to conduct a multi-center phase II randomized clinical trial of botulinum toxin type A (BoNT/A) for treating benign prostatic hyperplasia (BPH). This protocol describes the background, design, and organization of the trial.

The protocol was written by the members of the BPH Study Group, approved by an External Review Board, and approved by the Institutional Review Boards (IRB) of each participating clinical center prior to the initiation of recruitment.

The primary objective of this study is to determine whether two different doses of BoNT/A injection into the prostate gland demonstrate sufficient improvement in the management of lower urinary symptoms due to BPH to warrant more extensive research. The secondary aims are to:

- examine evidence of toxicity and side effects due to the local BoNT/A injection into the prostate;
- examine the durability of effects;
- observe the effect of BoNT/A injection on the overall reduction in size of the prostate gland;
- select the drug dose that would be most effective as a comparator arm in a future phase III randomized clinical trial.

## 2 Background and Significance

Investigators and health providers continue to seek therapies for lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) that provide improved relief of symptoms and a lower side effect profile. The ideal therapy for relief of LUTS secondary to BPH would carry a high success rate, be noninvasive, durable, and low cost. Intraprostatic injection for BPH has intrigued investigators for more than 100 years as a possible less invasive therapy for BPH. There are advantages and disadvantages associated with each route of injection [Plante et al. 2004]. While the transperineal, transrectal, and transurethral routes have been explored over time, a review of the literature on intraprostatic injections would indicate that transperineal and transurethral injections have the most systematic evaluation. Most injectants produce prostate apoptosis and gland volume reduction with varying degrees of LUTS relief. Anhydrous ethanol was the most widely studied injectable, but large scale trials identified significant side effects, leaving the field to continue to search for other effective agents.

Success with botulinum toxin to treat non-prostate symptoms of the lower urinary tract provided evidence that botulinum toxin may offer relief of LUTS attributed to BPH [Cruz and Silva 2004]. Approximately 70% of men with bladder outlet obstruction (BOO) will have some symptoms of overactive bladder (OAB). The exact pathophysiology of OAB in BOO is unknown; evidence points to changes in both the efferent and afferent innervation and the detrusor [Kavia and Mumtaz 2005]. Surgical denervation is known to produce profound atrophy of the rat prostate. Botulinum toxin type A (BoNT/A) injection into the rat prostate gland induces selective denervation and subsequent atrophy of the prostate at all doses. Apoptosis was seen diffusely throughout the gland. There were no significant complications (e.g., urinary retention, weight loss, or hind/limb weakness) and the authors concluded that this neurotoxin may represent a potential long acting therapy for the prostate [Doggweiler et al. 1998].

Recently, Chuang et al. [2006] injected up to 20 U BoNT/A into the prostates of 450-550 gm rats (~40 U/kg) and demonstrated a dose-dependent decrease in prostate size, increase in TUNEL staining, and decrease in proliferative cells and alpha-1A receptor staining observed at 1 week with recovery evident by week 2. They interpreted their findings as BoNT/A potentially regulating the static and dynamic components of BPH. Citing evidence that acetylcholine can regulate intracellular function [Ventura 2002], they postulated that the apoptotic changes and associated decrease in cellular

proliferation was due to local inhibition of acetylcholine release and subsequent neurotrophic effect on the innervated tissue.

This investigation proposes to determine the safety and efficacy of botulinum toxin injection for relief of BPH symptoms. The most potent natural toxins, the botulinum neurotoxins produced by clostridium bacteria, result in paralysis and death when administered at toxic doses. Botulinum toxin blocks acetylcholine release presynaptically in the neuromuscular junction. Physiologically, this produces a temporary denervation. The seven botulinum neurotoxins all act by targeting the same vesicle fusion machinery, and yet they cause paralysis of different durations [Davletov et al. 2005]. Clinically, the toxic effects of botulinum toxin are controlled and directed to treat medical conditions characterized by excessive muscle contraction (both involuntary activity and increased muscle tone), and through other theoretical mechanisms, to produce pain relief. Muscle relaxation occurs within a few days to 1 week after local injection, peaks within 2 weeks for several weeks, and then plateaus in milder form (the desired clinical effect) before gradually returning to baseline. Recovery from toxin-induced relaxation involves resprouting of terminals from the axon, followed by slow recovery of the neuron's ability to release acetylcholine [DePaiva 1999; Blitzer and Sulica 2001; O'Day 2001]. When administered to skeletal muscle, the clinical effects typically last for 3 to 4 months after each injection. The dose administered affects both the intensity of denervation and the length of the initial and plateau periods [Bell et al. 2000; Blitzer and Sulica 2001; Brashear 2001; Mahant et al. 2000; Tsui 1996].

Recent evaluation of botulinum toxin injection into the prostates of monkeys using multiple injections has identified the formation of bladder calculi on follow-up studies. The injection was performed by suprapubic puncture and the stones were identified in several monkeys. The significance of this finding is unclear at this time.

### 2.1 Use of Botulinum Toxin for Non-BPH Conditions

Botulinum toxin injection was first used in the 1970s to treat strabismus, and studies have shown that botulinum toxin type A reduces ocular deviation in more than 50% of patients [Flanders et al. 1987; Lennerstrand et al. 1998; Petitto and Buckley 1991; Scott 1980]. Adverse events following botulinum toxin injection were rare and typically temporary (transient ptosis, subconjunctival hemorrhage, and transient vertical deviations of the globe) [Münchau and Bhatia 2000; Tsui 1996]. Today, the type A toxin (Botox®, Allergan Pharmaceuticals, Irvine, CA) is approved for the treatment of strabismus, blepharospasm, seventh cranial nerve disorders (hemifacial spasm), cervical dystonia, axillary hyperhidrosis, and glabellar frown lines. The type B toxin (Myobloc in the US and NeuroBloc in Europe, Solstice Pharmaceuticals) is approved for the treatment of cervical dystonia. Outside the United States, a different preparation of the type A toxin (Dysport, Ispen, Ltd., Berkshire, UK) is available [Lew 2002]. There are numerous other potential uses under investigation including migraine [Conway et al. 2005; Dodick et al. 2005; Mathew et al. 2005], esophageal sphincter dysfunction [Murry et al. 2005], detrusor overactivity [Grosse et al. 2005; Kuo 2004; Reitz et al. 2004], leg spasticity [Rousseaux et al. 2005], dysgeusia [Eibling 2005], hyperhidrosis [Nelson et al. 2005], trigeminal neuralgia [Allam et al. 2005], chronic pain disorders [Jabbari et al, 2003; Lang 2003; Lew 2002; von Lindern et al. 2003], and anal fissures [Nelson 2003]. In some of these disorders, direct involvement of hyperactive muscles is difficult to demonstrate, suggesting that botulinum toxin may provide pain relief through interfering with the same mechanism of snare-complex mediated vesicular release in nerve terminals with other neurotransmitters [Aoki 2003].

While the mechanism of antinociceptive effect of BoNT/A is under investigation, similar pain relief has been noted in studies focused on chronic pain syndromes associated with lower urinary tract disorders. There are several proposed mechanisms of action by which relief of pain is achieved. These mechanisms would include:

- Decreased release of neuropeptides from nociceptive primary afferent nerve fibres in patients with interstitial cystitis [Maria et al. 1998].

- Noncholinergic neurotransmitter involvement, including modulation of substance P [Aoki 1998] based on the observation that pain relief in cervical dystonia exceeds the anticipated effect on the muscle and occurs prior to change in the muscular pattern [Brin et al. 1987]. These results suggest that mechanisms other than chemodenervation may be involved.
- A barrage of nociceptive information from the dysfunctional pelvic floor overflood the CNS and induce a changed CNS processing. Interrupting the efferent branch of the disturbed central circle may be responsible for interrupting the pain cycle [Zermann et al. 2000].

## 2.2 Use of Botulinum Toxin for BPH and its Symptoms

The relief of voiding dysfunction in benign prostatic hyperplasia (BPH) patients after intraprostatic injection of BoNT/A was based on the observation that, in rodents, the prostate undergoes atrophy after a local toxin injection, noted above [Doggweiler et al. 1998]. Maria and colleagues conducted a randomized, placebo-controlled study (4 mL saline solution in 15 men versus 200 U of botulinum toxin A in 15 men) in 30 consecutive men with BPH [Maria et al. 2003]. Men were injected using a perineal approach into prostate lobes under trans-rectal ultrasound (TRUS) guidance. Two months following injection, 13 patients in the treated group and 3 in the control group had subjective symptomatic relief ($p = 0.0007$). Other results are given in Table 1.

**Table 1. Change from baseline results of randomized placebo controlled study [Maria et al. 2003]***

| | Botulinum toxin | Control (saline) |
|---|---|---|
| symptom score | reduced by 65% from baseline | NSC** from baseline and 1 month follow-up |
| serum PSA | decreased 51% from baseline | NSC** from baseline and 1 month follow-up |
| Qmax | increased from 8.1 to 15.4 ml/s | |
| PVR urine | decreased from 126 to 21 ml | |
| prostate size | decreased from 50 to 17 cc | |

* Follow-up averaged 19.6 +/- 3.8 months. No reported side effects.
** No Significant Change

Additional studies were non-randomized clinical trial conducted in men with urinary retention or men whose symptoms were refractory to medical therapy [Chuang et al. 2004]. Study sizes were smaller with 10 to 16 men, and the dose of botulinum toxin utilized varied from 100 to 200 units. However, in all studies, improvement in symptoms were noted within 1 week and maximal within 2 to 4 weeks. Further, the relief of symptoms occurred in all men and was durable. As a general pattern the storage symptoms improved more than voiding symptoms despite significant increase in Qmax.

Botulinum toxin for the relief of LUTS secondary to BPH has been successful in all studies reported to date. While these studies have small patient populations and follow-up is generally less than one year, the improvement in voiding parameters is superior to the outcomes historically attributed to medical therapy and similar to other MIST therapies. Further, the time interval to improved voiding appears to be shorter than the interval associated with other MIST therapies [Chuang et al. 2004; Maria et al. 2003; Wein 2005]. Results are reported in Table 2.

**Table 2. Results of non-randomized transperineal prostate injection of BoNT/A under TRUS guidance**

| | Pre-treatment | Post-treatment | Change (%) |
|---|---|---|---|
| Prostate volume (mean) | $19.6 \pm 1.2$ cm$^3$ | $17.0 \pm 1.1$ cm$^3$ | -13.3% |
| AUASS | $18.8 \pm 1.6$ | $8.9 \pm 1.9$ | -52.6% |

| | | | |
|---|---|---|---|
| QOL index | 3.8 ± 0.3 | 2.1 ± 0.3 | -44.7% |
| Qmax | 7.3 ± 0.7 mL/s | 11.8 ± 0.8 mL/s | +39.8% |

In 2 patients who underwent biopsy 1 month after BoNT/A injection, terminal deoxynucleotidyl-mediated deoxyuridine triphosphate nick end labeling staining demonstrated an increase in apoptotic activity, not only in the glandular component but also in the stromal component of the prostatic tissue. This experience indicates a promising treatment for patients with small prostates and symptomatic BPH [Chuang et al. 2005].

### 2.2.1 Prostate Size

Atrophy of the prostate tissue may be explained by the blockade of acetylcholine or epinephrine release from local parasympathetic and sympathetic efferent nerve fibers. However, without adequate histology of prostate specimens after BoNT/A injection, it is impossible to determine whether the gland atrophy was the result of a specific toxin action or was merely caused by a non-specific effect of the injected fluid. It should also be recalled that prostate shrinkage was not reported in the study by Chuang et al. [2004], although the authors used only 100 U of BoNT/A, much less than the dose used in the study by Maria et al. [2003].

### 2.2.2 Routes of Injection

The ideal route of administration of botulinum toxin in the prostate has not been established. The practice of prostate injection therapy for BPH is not a new concept. The earliest prostate injection methodology employed transperineal injection of the prostate using the simultaneous digital rectal exam to guide therapy [Ambiavagar et al. 1975; Angell 1969; Bhargava et al. 1977; Broughton and Smith 1970; Kabra et al. 1977; Milroy 1968; Sharma and Goel 1977; Shipman and Akilie 1967; Talwar and Pande 1966]. More recent work improved the results of the transperineal technique when transrectal ultrasound guidance was used to visualize the injection of a small volume fluid [Chiang et al 2003; Maria et al. 2003; Savoca et al. 2001]. However, concern for possible extraprostatic leakage due to backflow along the needle tract remained [Shipman and Akilie 1967; Talwar and Pande 1966]. Alternative access sites for prostate injection, such as transurethral and transrectal, are clinically (and in large part anecdotally) associated with greater patient comfort, improved ability to target a given location within the prostate, or decreased complication rate.

- *Transrectal*. There are a very limited number of papers that describe the use of transrectal intraprostatic injection for the treatment of BPH [Larson and Huidobro 2001/A47; Larson et al. 2001/A132]. In many respects, this is surprising given the fact that transrectal biopsy of the prostate is one of the most common office based procedures in the urology office. Transrectal ultrasound and biopsy of the prostate is often preceded by transrectal ultrasound guided infiltration of the lateral pedicles of the prostate for prostate anesthesia. This technique is associated with the highest accuracy to locate a specific structure within or adjacent to the prostate. The theoretical concerns for fistula formation found in early reports have not materialized. Further, the equipment to accomplish this technique is readily available. While formal studies reporting the transrectal technique for injection are lacking, the technology, familiarity with the technique, and the safety associated with prostate nerve block support additional investigation of this approach. More importantly, transrectal ultrasound guidance provides the greatest level of reproducibility to inject a given target location.
- *Transurethral*. The interests of transurethral absolute ethanol injection for the treatment of BPH, alone and in combination with RF ablation of the prostate, stimulated development for the transurethral injection technique. One technique employed a straight needle with injection cystoscopically into the lateral prostate lobes [Goya et al. 1999]. Alternate approaches advocated

the use of a curved hollow core needle to penetrate the lateral lobe tissue [Plante et al. 2002]. An adaptation of the curved needle system is now available commercially (with a detente system for graduated needle deployment) as ProstaJect ethanol injection therapy system (American Medical Systems, Minnetonka, Minnesota). Subsequent studies with this device provide the largest experience with intraprostatic injection therapy [Ditrolio et al. 2002; Ditrolio et al. 2003; Plante et al. 2003]. When compared to transperineal injection, the transurethral injection was reported to offer increased safety, presumably because the integrity of the prostate capsule remains intact [Adams et al. 2000; Plante et al. 2003; Zvara and Plante 2000]. However, the ability to inject a very specific location with a high degree of reproducibility is limited without ultrasound guidance. Depth of needle penetration, cephalad/caudal migration, as well as anterior/posterior orientation are not controlled as accurately under endoscopic guidance as they would under transrectal guidance.

### 2.3 Summary

After a decade of wide ranging therapeutic applications, the commercially available BoNT/A is well tolerated across a range of doses. There are also no reports in the literature about acute complications related to the injection of this toxin into the lower urinary tract, such as general paralysis, alterations in the electrical myocardial conduction or respiratory depression [Bakheit et al. 2001; Borodic et al. 1996; Greene et al. 1994; Phelan et al. 2001; Schurch et al. 2000; Zermann et al. 2000]. A recent study demonstrated no local or systematic side effects in 15 patients with BPH after injection of botulinum toxin A. Moreover, they reported a 68% and 83% reduction in prostate volume and postvoid residual volume in treatment and control groups, respectively [Maria et al. 2003].

Because of the proven effectiveness and safety of botulinum toxin injection in a wide range of applications in the urological field, it seems that this toxin can reverse the obstructive urinary symptoms caused by BPH through decreased neuro-muscular hypertonicity of the prostatic smooth muscle cells and possibly other unidentified mechanisms. It may also reduce the prostatic volume by the involution of the epithelial component [Chuang et al. 2006].

This randomized phase II trial was developed to demonstrate whether botulinum toxin is potentially useful in the management of BPH. The doses, duration of the effect, improvement of symptoms, and effect on prostatic volume are evaluated in this study.

## 3 Study Design

This is a non-comparative phase II study in patients who have lower urinary symptoms due to BPH. Patients are randomized to one of two doses of botulinum toxin, either a 100 U dose or a 300 U dose. For each drug dose, an optimal two-stage design is then used to determine whether there is sufficient response to the treatment (i.e., whether the dose level is 'active'). The decision of whether or not to terminate after the first stage is based on the number of successes observed for the patients in the first stage, given that there are no safety concerns. Success is defined as the occurrence of either one or both of the following:

- Improvement in the AUA symptom score index by 30% from baseline within the first 12 weeks after injection.
- Qmax improvement of more than 30% from baseline within the first 12 weeks after injection.

### 3.1 Recruitment

Patients are recruited through the patient populations of the 7 clinical centers of the NIDDK supported BPH Study Group consortium. By the nature of the disease, all patients are male and the disease occurs principally in men over the age of 50, so no children or women will be candidates for the study. There is no targeted race-specific recruitment.

Patient outreach via radio or television advertising or mass or targeted mailings may be used. Once an interested patient is identified, a verbal introduction to the study is presented by the principal investigator and/or other designated, study-related, qualified individual. The study coordinator or clinic nurse follows up with additional information regarding the research, with more details and potential risks and benefits. All questions and concerns are addressed to the satisfaction of the patient. The patient understands that he has the option to be managed with traditional invasive and non-invasive procedures and therapies for BPH.

## 3.2 Eligibility, Screening, and Informed Consent

### 3.2.1 Inclusion and Exclusion Criteria

- Inclusion:
  0. Male at least 50 years of age.
  1. Voided volume ≥ 125 ml.
  2. Maximum urinary flow < 15 ml/sec.
  3. AUA symptom severity score ≥ 8.
  4. Patient signed informed consent prior to the performance of any study procedures.
  5. Patient able to complete the study protocol in the opinion of the investigator.

- Exclusion:
  6. Any prior surgical intervention for BPH.
  7. Current diagnosis of acute or chronic prostatitis (which may cause LUTS that mimic BPH).
  8. Overactive bladder without bladder outlet obstruction.
  9. Enrolled in another treatment trial for any disease within the past 30 days.
  10. Men interested in future fertility.
  11. Previous exposure to botulinum toxin.
  12. On alpha-blocker within the past 48 hours.
  13. On any 5-alpha-reductase inhibitor within the past month.
  14. Post void residual > 350 ml.
  15. On phenylephrine, pseudoephedrine, imipramine, an anticholinergic, or cholinergic medication within the past 2 weeks.
  16. On estrogen, androgen, any drug producing androgen suppression, or anabolic steroids within the past 4 months.
  17. Clinically significant renal or hepatic impairment as determined by abnormal creatinine or AST levels (based on local institutional values).
  18. Serum prostate specific antigen level > 8 ng/ml (Hybritech). For those with a PSA between 4-8 ng/ml, the PSA elevation must be considered to be from a benign cause in the opinion of the PI. This decision can be based on PSA velocity, previous TRUS biopsy, percent free PSA, or other clinical estimations in keeping with sound urologic care.
  19. Active urinary tract disease or biopsy of the prostate within the past 6 weeks.
  20. Daily use of a pad or device for incontinence required.
  21. Episode of unstable angina pectoris, myocardial infarction, transient ischemic attack, or cerebrovascular accident (stroke) within the past 6 months.
  22. On aminoglycosides or any drug that interfere with neuromuscular transmission.
  23. Eaton-Lambert syndrome, hemophilia, hereditary clotting factors deficiency, or bleeding diathesis.
  24. Penile prosthesis or artificial urinary sphincter.
  25. History or current evidence of carcinoma of the prostate or bladder, pelvic radiation or surgery, urethral stricture, or bladder neck obstruction.

26. Known primary neurologic conditions such as multiple sclerosis, myasthenia gravis or Parkinson's disease, or other neurological diseases known to affect bladder function.
27. Documented bacterial or acute prostatitis within the past year.
28. Two documented urinary tract infections of any type in the past year (UTI defined as > 100,000 colonies per ml urine from midstream clean catch or catheterized specimen).
29. History of bladder calculi.
30. Patients must be off aspirin, NSAIDS, and Coumadin for 7 or more days prior to botulinum toxin injection.
31. Cancer that is not considered cured, except basal cell or squamous cell carcinoma of the skin (cured defined as no evidence of cancer within the past 5 years).
32. Any serious medical condition likely to impede successful completion of the study, such as certain mental disorders, hypersensitivity to botulinum toxin or anesthetics used in the study, syncope, uncontrolled diabetes.

### 3.2.2 Screening

Screening is accomplished in two visits. The first visit involves the informed consent form, medical history, blood draw, AUA symptom score, uroflow testing, post-void residual urine measurement, and vital signs. If all relevant eligibility criteria are passed, a second visit is scheduled to meet with the physician who performs a physical exam and digital rectal exam, and repeat AUA symptom score, uroflow testing, and post-void residual urine measurement. A maximum of 30 days is allowed between start of screening and administration of study drug.

### 3.2.3 Informed Consent

Consent is obtained in a quiet setting prior to the initiation of any study procedures, and the patient is given opportunity to delay consent until he has taken adequate time to read and understand the written consent and discuss the study with family and/or other physicians outside the clinic setting. The patient is fully informed about the possible risks of urinary retention, fecal incontinence, and infection as a result of intraprostatic botulinum toxin injection, as well as other risks associated with botulinum toxin that are addressed in the drug injection label. In addition, the patient is informed of the development of bladder calculi in experimental animals. Treatment options as a regular patient, including oral medication, other minimally invasive therapies, and surgery, are fully discussed prior to consent to participate in the trial.

Patients are not consented in writing until they demonstrate adequate understanding of all aspects of the study and consent process. Asking the patient to explain the study in his own words establishes his understanding. A copy of the consent form is given to the patient. The signed consent form remains in the patient's study files at the clinical center.

## 3.3 Randomization and Masking

Once eligibility criteria have been met, patients are randomized to one of the two treatment doses according to a randomization scheme generated by the coordinating center. The randomization scheme assigns equal numbers to each treatment group using methods that preclude the ability to guess the next assignment.

Both patient and study staff are masked to treatment group assignment. A clinical staff member who is not involved in patient evaluation or assessment reconstitutes the BoNT/A (see below) and prepares the syringe with the assigned concentration. The syringe has the same volume for either dose, and is labeled with the patient study ID.

### 3.4 Study Drug and Dose

Drug to be used: Botulinum toxin type A is marketed in two pharmaceutical distinct formulations that are not equipotent in terms of mouse units. Differences in species sensitivities to different botulinum neurotoxin serotypes preclude extrapolation of animal-dose activity relationships to human dose estimates. For the purposes of this study, patients are treated with the presentation of botulinum toxin type A which is marketed in the US as BOTOX® by Allergan. BOTOX® is a purified neurotoxin complex supplied as a sterile, vacuum dried purified botulinum toxin type A, produced from fermentation of Clostridium botulinum type A.

One unit of BoNT/A corresponds to the calculated median intraperitoneal lethal dose (LD 50) in mice. The specific activity of BoNT/A is approximately 20 units/nanogram of neurotoxin protein complex.

Supplier: Allergan, Irvine CA.

Clinical pharmacology: BoNT/A blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings.

When injected intramuscularly at therapeutic doses, BoNT/A produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extra-junctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by BTX in approximately 91 days.

When injected intradermally, BoNT/A produces temporary chemical denervation of the sweat gland, resulting in local reduction in sweating.

Pharmacokinetics: BoNT/A is not expected to be present in the peripheral blood at measurable levels following IM or intradermal injection at the recommended doses. The recommended doses of neurotoxin administered at each treatment session are not expected to result in systemic, overt distant clinical effects, i.e., muscle weakness, in patients without other neuromuscular dysfunction. However, some clinical systemic effects have been shown by a single fiber electromyography after IM doses of botulinum toxins appropriate to produce clinically observable local muscle weakness.

Contraindications: BoNT/A is contraindicated in the presence of infection at the proposed injection site(s), and in individuals with known hypersensitivity to any ingredient in the formulation.

Formulation: BoNT/A is supplied in a single-use vial. Each vial contains 100 units of vacuum-dried Clostridium botulinum type A neurotoxin components (NDC 0023-1145-01).

Storage and stability: Unopened vials of BoNT/A should be stored in a refrigerator (2° to 8° C) for up to 24 months (or the expiration date on the product label). Administer BoNT/A within four hours of reconstitution and within 30 minutes of drawing into syringe; during this period the reconstituted BoNT/A should be stored in a refrigerator (2° to 8° C).

Dilution technique: Prior to injection, reconstitute vacuum-dried BoNT/A with sterile normal saline without a preservative; 0.9% sodium chloride injection is the only recommended diluent. Draw up the proper amount of the diluent in the appropriate size syringe, and slowly inject the diluent into the vial. Record the date and time of reconstitution on the space on the label.

- To reconstitute BoNT/A 100 U, add 4 ml of normal saline to the vial. The resulting 4 ml equals 100 U in the syringe.

- To reconstitute BoNT/A 300 U, three 100 U vials are needed. Dilute each 100 U vial with 1.3 ml of normal saline. Each reconstituted vial is then drawn up into a single syringe with a total of 4 ml = 300 U.

Instruments: The instrument used to inject the botulinum toxin is an ultrasound device with a transrectal ultrasound probe specially designed for prostate biopsies which has a special canal to introduce and direct a needle in to the selected prostatic area. This device is regularly used to work-up patients with BPH and make biopsies when needed.

Administration: Because botulinum toxin type A solution does not contain a preservative, it should be administered within 4 hours after reconstitution and within 30 minutes of drawing into the syringe. The drug should be stored in a refrigerator when not in use during this period.

- Patient Preparation
  - Patient is examined and submits urine for urinalysis which is examined by standard dipstick analysis or microscopic examination prior to randomization and preparing BoNT/A solution to ensure that no infection is noted or suspected.
  - Patient is dosed with a single dose of appropriate broad-spectrum antibiotics the morning of the procedure according to the clinical practice of the center PI.
  - Prostate size is measured via transrectal ultrasound on patients after receiving a Fleet's enema the morning of the examination. The patient is placed in the lateral decubitus position with knees tucked against the chest and the transrectal probe introduced. A multi-planar probe that gives a 112° sector image is used to allow viewing in both transverse and longitudinal planes without moving the probe. The prostate size is measured initially using the height (H), width (W), and length (L) functions available on the ultrasound machine. Scanning of the prostate is carried out in two planes at right angles to each other. The height and width are identified on a transverse image and recorded. The length is identified and recorded in the perpendicular longitudinal plane. The volume is calculated as a machine function using the formula H x W x L x $\pi/6$ and recorded on hard copy.
- Botulinum Toxin Injection
  - Anesthesia is delivered according to the clinical practice of the center PI. Transrectal periprostatic block may be used with a 5 ml bolus of 1% lidocaine given just superiolateral to each seminal vesicle as visualized using the transrectal sound probe in the sagittal plane. The bolus is given via an appropriately long 22-gauge needle.
  - The botulinum toxin type A solution is given via the same approach using a second needle.
    - For men randomized to the 100 unit arm, 25 units per 1.0 ml volume is given at the following points of the transitional zone: left and right inferior and superior transitional zone.
    - For men randomized to the 300 unit arm, 75 units per 1.0 ml volume is given at the following points of the transitional zone: left and right inferior and superior transitional zone.
  - The needle is passed from posterior to anterior through the peripheral zone (PZ) into the base of the prostate at the transition zone/central zone junction on the left side. The needle is advanced to superior aspect of the transition zone.
  - Prior to injection of botulinum toxin the needle is aspirated to insure that there is no blood return. This is repeated prior to each injection.
  - The initial 1.0 ml of solution is first deposited at the superior (bladder base) transition zone (TZ). The needle is withdrawn to the inferior (apex) transition zone/central zone junction and the second 1.0 ml of solution is deposited on the same side as the needle is withdrawn.

- The needle is passed from posterior to anterior through the peripheral zone (PZ) on the right side into the base of the prostate at the transition zone/central zone junction on the left side. The needle is advanced to superior (bladder base) aspect of the transition zone.
- The 1.0 ml of solution is first deposited at the inferior (apex) transition zone (TZ). The needle is withdrawn to the inferior (apex) transition zone/central zone junction and the second 1.0 ml of solution is deposited on the same side as the needle is withdrawn.
- The needle, syringe, and vial are disposed of in a biohazard container according to institutional policy, and a witness signs a form.
- After the injection, the patient remains in the clinic until a spontaneous void has occurred.
- Because of the theoretical possibility of diffusion of botulinum toxin into seminal fluid, and no evidence to the contrary, those patients who engage in sexual intercourse are required to use condoms for 48 hours after the injection.

Overdose: Signs and symptoms of botulinum toxin type A overdose are not apparent immediately after injection. If accidental injection occurs, medical supervision should be provided for up to several weeks to detect signs and symptoms of systemic weakness or muscle paralysis. An antitoxin is available if an overdose occurs or the drug is inadvertently administered in an improper manner (misinjection) and the incident is promptly discovered.

An antitoxin is available through the U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention (CDC). In the event of an overdose or injection into the wrong muscle, study staff immediately contacts Allergan. Allergan representatives immediately call the corresponding state health department emergency 24-hour telephone number. The state health department contacts the CDC to arrange for a clinical consultation by telephone and, if indicated, release of botulinum antitoxin. The antitoxin does not reverse any signs or symptoms of botulism toxin induced muscle weakness already apparent by the time of antitoxin administration.

The administration of antitoxin therapy is the only specific therapy available for botulism, and evidence suggests it is more effective if undertaken early in the course of neurological dysfunction [Tackett et al. 1984]. This is not surprising when one considers that equine antitoxin neutralizes only toxin molecules yet unbound to nerve endings [Sugiyama 1980]. More than 80% of persons reported with adult botulism in the United States are treated with antitoxin. Before administration of antitoxin, skin testing should be performed to test for sensitivity to serum or antitoxin. Administration of one 10-ml vial of trivalent botulism antitoxin given by the intravenous route results in serum levels of type A, B, and E antibodies capable of neutralizing serum toxin concentrations in excess of those reported for botulism patients. Therefore, after skin testing for sensitivity, contrary to the antitoxin package insert, administration of one vial of antitoxin intravenously is recommended and antitoxin need not be repeated since the circulating antitoxins have a half-life of 5-8 days [Hatheway et al. 1984]. However, treatment is not without risk, as approximately 9% of persons treated experience hypersensitivity reactions [Black and Gunn 1980]. It is therefore extremely important that physicians recognize botulism symptoms as early in its course as possible, and yet not mistake other neurologic syndromes for botulism.

Systemic side effects: The risk of generalized paralysis after GU application of BoNT/A has never been reported. However, the risk of generalized paralysis is felt to be unlikely because the total dose administered is one tenth of the presumed lethal dose. There is one report of mild muscular weakness in upper extremities 2 weeks to 3 months after bladder injection of 1000 U Dysport and additional monitoring is warranted [Del Popolo et al. 2004]. Note that one U of BOTOX is not equal to one unit of Dysport.

Toxicity: There have been rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility, after treatment with botulinum toxin. There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial

infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established. The following events have been reported since the drug has been marketed and a causal relationship to the botulinum toxin injected is unknown: skin rash (including erythema multiforme, urticaria and psoriasiform eruption), pruritus, and allergic reaction.

In general, adverse events occur within the first week following injection of BoNT/A and while generally transient may have a duration of several months. Localized pain, tenderness and/or bruising may be associated with the injection. Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of adjacent muscles may also occur due to spread of toxin.

### 3.5 Primary and Secondary Outcomes

The primary objective of this randomized phase II trial is to determine whether two different doses of botulinum toxin type A (BoNT/A) injection into the prostate gland demonstrate sufficient improvement in the management of lower urinary symptoms due to BPH to warrant more extensive research. If both doses pass the criteria for successful response rate, then comparison based on secondary outcomes determines the more effective or durable dose to be used in a future phase III randomized clinical trial.

The primary outcome is the proportion of patients who are treated successfully. The treatment is considered successful if either or both of the following occur:

- Improvement in the AUA symptom score index by 30% from baseline within the first 12 weeks after injection.
- Qmax improvement of more than 30% from baseline within the first 12 weeks after injection.

Major secondary outcomes include the following:

- evidence of toxicity and side effects,
- durability of effects,
- improvement in urinary frequency,
- prostate volume change from baseline, and
- post-void residual urine.

### 3.6 Data Collection and Procedures Schedule

In this randomized phase II trial, patients are contacted by phone at 1 week and evaluated in clinic at 4, 8, and 12 weeks, 6, 9, and 12 months. The procedures to be completed in this study and frequency that they will be performed are in Table 3. All the procedures performed in this study are normally done in the work-up of patients diagnosed with BPH. The only procedure/treatment which is not routine is the injection of botulinum toxin. It is important to adhere to the trial plan as closely as possible. Any study procedure, treatment, or visit should occur within three days of the scheduled date.

**Table 3. Data Collection Procedures and Schedule**

| | Screen ⇐ *max 30 days* ⇒ | Tx (0) | 1 wk | 4 wk | 8 wk | 12 wk | 6 mo | 9 mo | 12 mo |
|---|---|---|---|---|---|---|---|---|---|
| Informed consent | 1 | | | | | | | | |
| Eligibility | 1,2 | | | | | | | | |
| Medical history | 1 | | | | | | | | |
| Physical and digital rectal exam | 2 | | | | | X | X | | X |
| Labs: urinalysis | 1 | X | | X | X | X | X | | X |
| Labs: hematology, serum chemistry (a) | 1 | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Labs: PSA | 1 | | | | | X | X | | X |
| Urodynamic function (uroflowmetry, PVR) | 1,2 | | | X | X | X | X | X | X |
| Vital signs (BP, HR) | 1 | X | | X | X | X | X | X | X |
| AUA symptom score | 1,2 | | | X | X | X | X | X | X |
| Function battery (b) | 2 | | | | | X | | | X |
| TRUS | | X | | | | X | | | X |
| Bladder ultrasound | 2 (d) | | | | | | | | X |
| Botulinum toxin injection | | X | | | | | | | |
| 3-day voiding diary | | X | | | | X | | X | X |
| Follow-up (c) | | | X | X | X | X | X | X | X |

(a) serum chemistries are sodium, potassium, chloride, carbon dioxide, glucose, creatinine, BUN, AST
(b) surveys of BPH impact scale, bladder function, erectile function, and ejaculatory function
(c) new diagnoses, treatments, life events, concomitant meds, adverse events
(d) or cystoscopy performed no more than 6 weeks prior to baseline

### 3.7 Retention and Dropout/Withdrawal

Minimal dropout or loss to follow-up is expected in this cohort, especially within the first 12 weeks to assessment of primary outcome. However, if a patient drops out before 12 weeks, he is replaced for non-comparative dose-evaluation purposes so that the required sample size is realized. For purposes of tracking the feasibility of conducting a trial of treatment with BoNT/A, reasons for dropout or withdrawal is documented.

### 3.8 Patient Care and Management

The participant is contacted by phone at week 1 to collect medical events and status. Clinic visits are scheduled at 4, 8, and 12 weeks and 6, 9, and 12 months following injection. Additional contacts and visits for patient care and management are made as needed according to general clinical practice.

### 3.9 Patient Compensation

The study group may consider compensation as needed for travel and other expenses incurred as a result of participating in the study. Items of nominal value are distributed at visits to thank patients for their participation. All plans for compensation are approved by the local IRB.

### 3.10 Patient Privacy and Confidentiality

All data are labeled with the study ID, including forms and specimens. All data transferred to the coordinating center for accumulation in the central database identify the patient only with the study ID and acrostic. The coordinating center does not receive any personal identifiers.

Each field center maintains a file on each patient that includes personal identifiers, linking name and contact information to the study ID. These data are not entered into the study data management system or into any file on the study-dedicated computer supplied by the coordinating center. Patient files are kept in secure locations and the clinical center is responsible for taking every other reasonable measure (those set by the state, the site, and the study) to ensure and maintain record confidentiality and patient privacy.

## 4 Data Processing and Management

Data from the clinical centers and central labs are accumulated in a central database at the coordinating center. The coordinating center can accommodate data entered and transferred in a variety

of formats. Remote data entry and management systems developed and provided by the coordinating center may be (1) written in commercial data management system software installed on dedicated study computers, (2) accessed from the study secure website, or (3) collected and extracted from devices such as a tablet or palm pilot. Quality control procedures are pre-programmed depending on the technology. These include programmed skip patterns, range checks, and miscodes for multiple choice items.

Data are entered centrally or at the remote sites and transmitted to the central database at the coordinating center. Double data entry verification is used if needed to ensure accurate data entry. Data are received from sites in electronic format specific to the technologies and systems in place at each institution. The coordinating center receives data in computer-readable format. The coordinating center merges newly received data with the accumulated central database maintained on the Biostatistics Center's server.

Database quality control performed at the coordinating center includes range checks, inter-item checks, cross-table checks, and missing, incorrect, or questionable values. The coordinating center generates queries for the clinical center regarding data issues and quality. Query edit reports with the necessary patient identifying information and problem values are sent to the clinical centers for resolution. Corrected values are entered and checked again for consistency with other items. The goals are to make quality control a continuous process, to make the turnaround time between error detection and correction as short as possible, and to document any changes made to the database.

The Biostatistics Center's data backup and security policies ensure the safety and confidentiality of the data. Backup procedures include twice weekly system backup, daily incremental backup, and off-site fireproof storage. Security procedures include logon and link password protection, remote password logon and dial-back modems, and for internet access, separate web servers which use SSL and encryption algorithms. Regularly updated virus scanning software is used routinely to check personal computers for computer viruses. University computing facilities provide support in the event of a disaster.

The coordinating center maintains confidentiality of patient data and emerging results per a confidentiality policy, which every staff member is required to sign annually.

# 5 Safety and Monitoring

## 5.1 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board consisting of appropriately qualified independent experts is appointed by the NIDDK to provide review of data on patient safety and study progress. The purpose of the DSMB is to assure independent review as to whether study patients are exposed to unreasonable risk because of study participation, and to monitor study progress and integrity. DSMB members are chosen by NIDDK, and the DSMB determines a report format and reporting frequency before the start of data collection. The coordinating center provides reports on adverse events to the DSMB, including summary tabulations and narrative summaries on individual events.

The purpose of safety reports is to present the DSMB with information regarding adverse events experienced by study patients as a result of undergoing the study procedures. Clinical centers report adverse events to the coordinating center in a timely fashion, including a narrative summary of the event as well as indication of the duration, perceived relationship to the study procedures, and resolution. The coordinating center summarizes and reports adverse events to the DSMB. Severe or unexpected adverse events are reported immediately to the NIDDK and DSMB.

A summary of DSMB deliberations is prepared by NIDDK and distributed to the clinical centers to submit to their IRB.

## 5.2 Risks, Side Effects, Adverse Events, and Serious Adverse Events

Results of clinical observations, laboratory tests, and reported events form the basis for evaluating the safety profile of this therapy.

General risks: Botulinum toxin is contraindicated in the presence of infection at the proposed injection site(s), and in individuals with known hypersensitivity to any ingredient in the formulation.

There have been rare, spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis after treatment with botulinum toxin. These events have occurred in less than 1% of all patients treated and have not been reported in patients receiving botulism toxin type A for lower urinary tract symptoms. There have been additional rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. These side effects were noted in less than 1% of patients. The exact relationship of these events to the botulinum toxin injection has not been established.

The following events have been reported since the drug has been marketed, and a causal relationship to the botulinum toxin injected is unknown: skin rash (including erythema multiforme, urticaria, and psoriasiform eruption), pruritus, and allergic reaction.

In general, adverse events occur within the first week following injection of BoNT/A and while generally transient may have a duration of several months. Localized pain, tenderness, and/or bruising may be associated with the injection. Local weakness of the injected muscles, represents the expected pharmacologic action of the botulinum toxin. However, weakness of the adjacent muscles may also occur due to spread of toxin.

Risks associated with injection into the prostate: There is limited information about the potential risks associated with injections of BoNT/A into the prostate. There is little risk of affecting neighboring striated or visceral smooth muscle or even ganglionic transmission. Botulinum toxin does not penetrate the blood-brain barrier in doses used therapeutically. There is therefore no significant risk that transmitter function in the central nervous system will be affected. Botulinum toxin in doses used clinically has been a highly selective and safe neurotoxin.

Side effects: Side effects are monitored and include:

- Development of urinary incontinence or increase in subjects with previously established urinary incontinence due to BPH.
- Any degree of rectal incontinence.
- Any distant or regional muscle paralysis or weakening.
- Any neurological event related with the use of this drug.
- Any allergic reaction, local or systemic, due to botulinum toxin.
- Any case of viral diseases or Creutzfeldt-Jacob disease due to albumin.

Adverse events: An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event (AE) 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.

Adverse events related to the use of the needle into the prostate gland via transrectal ultrasound have been adopted using data from transrectal ultrasound biopsy reports, namely, prostatic infection or sepsis has been seen in less than 1% of the patients who undergo transrectal ultrasound biopsy. Pain and rectal discomfort may be present the first 24 hrs after the procedure. Between 14 to 58% of the patients could present hematuria and 6 to 28% of the patients could present hematospermia after the procedure. This is self limiting and does not put at risk the well-being of the subjects.

The patient is instructed to contact the study investigator or nurse coordinator with any concerns or problems, or to notify that an adverse event has occurred. In addition, the patient is asked about symptoms and events at each follow-up contact. Data are captured on an adverse events report form.

Supporting documentation (hospital notes, lab reports, etc.) is provided as needed. The clinical center coordinator 'sanitizes' all supporting documents by removing personal patient identifying information and labeling with the patient's study ID. All adverse events are reported whether expected (side effects) or unexpected and regardless of any perceived relationship to study treatment.

Serious adverse events: Additional procedures are warranted for cases of adverse events that are serious. As defined by the FDA, the event is serious and should be reported when the patient outcome is: (1) death; (2) life-threatening, i.e., the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death; (3) hospitalization (initial or prolonged); (4) disability, i.e., resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life; (5) congenital anomaly, i.e., there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child; (6) requires intervention to prevent permanent impairment or damage. Serious adverse events are reported immediately to the coordinating center, the NIDDK project office, the DSMB chair, and Allergan. The entire DSMB confers if needed.

### 5.3 Risk Management and Minimization

The safe and effective use of BoNT/A depends upon proper storage of the product, selection of the correct dose, proper reconstitution and administration techniques. The physicians and staff participating in this trial are trained in the proper storage, reconstitution of BoNT/A, and administration techniques. The physicians administering BoNT/A understand the relevant neurovascular and prostate anatomy of the area involved. BoNT/A treatment will not be administered in the presence of acute prostatitis, infection, or altered prostate anatomy.

This study is designed to minimize the risk to the patient. The study has been designed after a thorough review of the literature and evaluation by the BPH Study Group Steering Committee. Careful patient inclusion and exclusion criteria are used to minimize patient risk of side effect from the investigational agent.

Patients complete a clinical evaluation consistent with the standard of care in urology for the evaluation of lower urinary tract symptoms attributed to benign prostate hyperplasia. Further, patients receive prophylactic antibiotics consistent with the clinic standard operating procedure following transrectal ultrasound with biopsy.

Physicians performing transrectal ultrasound with BoNT/A injection have demonstrated expertise in transrectal ultrasound. Each physician performing these procedures has performed no less than 20 transrectal ultrasound evaluations of the prostate with biopsy. The techniques used to biopsy the prostate are the same used to inject the BoNT/A agent.

The drug dose selected for injection was selected after review of the literature. The drug dose was chosen to optimize potential for therapeutic benefit while minimizing risk for side effect. Further, the route of injection was chosen because the technique is acceptable for introducing materials into the prostate, and physicians are familiar with as it is almost identical to transrectal ultrasound with biopsy of the prostate. The typical urologist performs transrectal ultrasound of the prostate with biopsy in the clinic. Incorporating this familiar procedure allows the patient to receive a prostate anesthetic by injecting the superior neurovascular pedicle with a short acting anesthetic agent such as 1 % injectable lidocaine. The use of a local anesthetic improves patient comfort and is associated with increased patient satisfaction.

The study has been designed to provide close follow-up of participants to assure patient safety and monitor for study outcomes. If, at the end of the 12-week stage 1, one of the two dose arms is dropped, then the patients who were assigned to the arm continue to be followed to 1 year even though no additional patients are recruited for that arm. Patients are provided with a phone number that may be used 24 hours a day, 7 days a week to contact study personnel.

## 6 Statistical Issues

Patients are randomized to one of two doses of BoNT/A using block randomization.

Simon's optimal two-stage design is applied to determine whether there is sufficient activity at either of the two dose levels to warrant further investigation [Simon, 1989]. Each patient is considered either a successful or failed response based on the primary outcome criteria. The response rate or proportion of patients treated successfully is examined in two stages. The decision of whether or not to terminate after the first stage is based on the number of responses observed for the patients in the first stage. The procedure is termed 'non-comparative' because the two dose levels are not compared to each other but to a pre-determined critical cut-off value.

Four design parameters are specified to determine the optimal design for controlling the type I and type II error rate and minimizing the expected sample size when the true response rate is a specified value, p. These values are $\alpha$, the probability of concluding the response rate is acceptable for further study of the drug when it is actually too low; $\beta$, the probability of concluding the response rate is too low to warrant further study of the drug when it is actually acceptable; $p_0$, an uninteresting response rate; and $p_1$, the minimal clinically significant response rate.

For this study, we assume $\alpha$=.05, $\beta$=.10, $p_0$=.30, and $p_1$=.50. Based on these assumptions, the optimal two-stage design is the following:

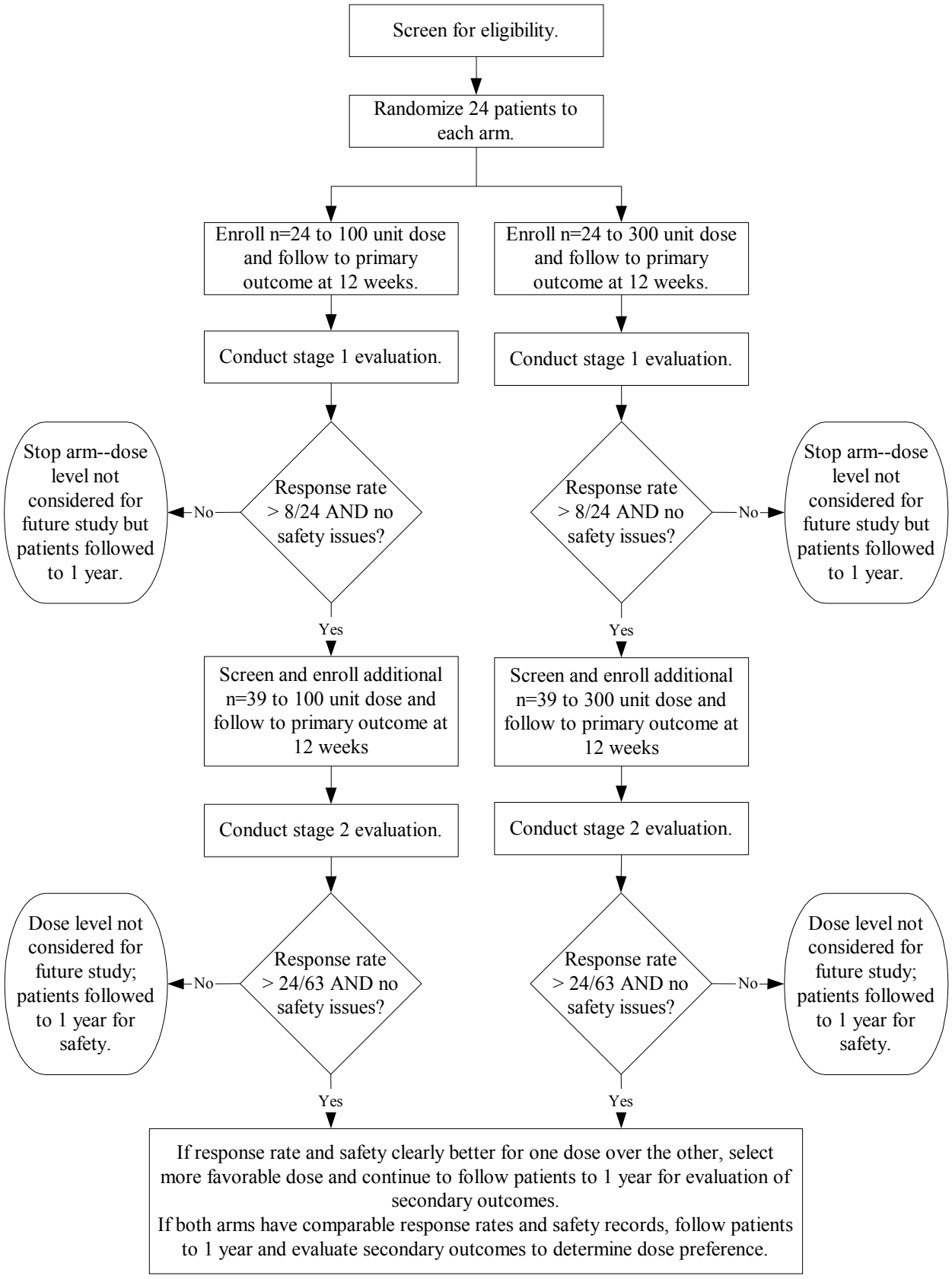
- Stage 1: For each dose, after 24 patients have reached the primary outcome at 12 weeks, at least 9 of 24 must be treated successfully to continue to stage 2 for that dose.
- Stage 2: For each dose, after 63 patients have reached the primary outcome at 12 weeks, at least 25 out of 63 must be treated successfully to warrant further testing.

In addition to examining the response rate at each stage, safety criteria must also be met for the dose to be acceptable. Safety criteria are based on occurrence of toxicity related to study therapy evaluated by grade, where 1 = mild side effect, 2 = moderate side effect, 3 = severe side effect, 4 = life threatening or disabling side effect, and 5 = fatality.

- In the case of a reported grade 4 or 5 toxicity, participant accrual is put on hold pending DSMB review of the event and relationship to botulinum toxin injection.
  - If the event is not related to botulinum toxin injection, participant accrual continues.
  - If the event is related to botulinum toxin injection, the dose arm is terminated.
- Participant accrual to a dose arm is terminated if ≥ 40% of the participants report a grade 2 or 3 toxicity related to the botulinum toxin injection.
  - In stage 1, if 10 participants report grade 2 or 3 toxicity the dose arm is terminated.
  - In stage 2, if 26 participants report grade 2 or 3 toxicity the dose arm is terminated.

Each drug dose is evaluated independently. If both doses achieve acceptable response rates and demonstrate no safety considerations, the dose which is most promising based on relative response rate, safety, reduction in prostate size, and durability of response is selected for future study.

The process is summarized in the figure.


Screen for eligibility.
Randomize 24 patients to each arm.
Enroll n=24 to 100 unit dose and follow to primary outcome at 12 weeks.
Enroll n=24 to 300 unit dose and follow to primary outcome at 12 weeks.
Conduct stage 1 evaluation.
Conduct stage 1 evaluation.
Response rate > 8/24 AND no safety issues?
Response rate > 8/24 AND no safety issues?
No
Stop arm--dose level not considered for future study but patients followed to 1 year.
No
Stop arm--dose level not considered for future study but patients followed to 1 year.
Yes
Yes
Screen and enroll additional n=39 to 100 unit dose and follow to primary outcome at 12 weeks
Screen and enroll additional n=39 to 300 unit dose and follow to primary outcome at 12 weeks
Conduct stage 2 evaluation.
Conduct stage 2 evaluation.
Response rate > 24/63 AND no safety issues?
Response rate > 24/63 AND no safety issues?
No
Dose level not considered for future study; patients followed to 1 year for safety.
No
Dose level not considered for future study; patients followed to 1 year for safety.
Yes
Yes
If response rate and safety clearly better for one dose over the other, select more favorable dose and continue to follow patients to 1 year for evaluation of secondary outcomes.
If both arms have comparable response rates and safety records, follow patients to 1 year and evaluate secondary outcomes to determine dose preference.

## 7 Organization and Administration

The BPH Study Group is composed of investigators and study staff from the NIDDK project office, the study chair, the coordinating center at the George Washington University Biostatistics Centers, and the 7 clinical centers: Baylor College of Medicine, Cornell University, Mayo Clinic, Medical College of Wisconsin, Northwestern University, University of Colorado Health Science Center, and University of Texas Southwestern Medical Center. Organizationally:

- The Steering Committee is the primary decision making body for the study, and convenes periodic meetings and conference calls to review scientific issues and study progress. Members of the Steering Committee are the study chair, the principal investigators from each of the clinical centers and the coordinating center, and the NIDDK project office representative.
- The clinical centers are responsible for recruiting and enrolling patients and for collecting and entering data.
- The NIDDK project office participates in all decision-making activities and selects and oversees the activities of the Data Safety Monitoring Board.
- The Data Safety Monitoring Board (DSMB) is a group of independent experts assembled by the NIDDK to review reports of study progress, data quality, and patient safety, and advise the NIDDK on findings about study performance and patient safety.
- The coordinating center is responsible for statistical aspects of study design and conduct, implements and maintains the data management system, designs and monitors quality control systems, and makes administrative arrangements for the study group. The coordinating center produces performance reports, including periodic tracking reports and reports to the Steering Committee and Data Safety Monitoring Board.

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