IS LESS MORE?
DOES DECREASING ONABOTULINUMTOXINA INJECTION SITES IN THE BLADDER INCREASE PATIENT SATISFACTION WHILE MAINTAINING EFFICACY?

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PROTOCOL DATE: JANUARY 24, 2020

VERSION: 6

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IRB NUMBER: 2018-119
IRB APPROVAL DATE: 02/03/2020

I. Abbreviations

AE	Adverse Event
AUA	American Urological Society
BTX	OnabotulinumtoxinA
CRQIP	Clinical Research Quality and Process Improvement Program
FDA	Food and Drug Administration
GRA	Global Response Assessment
ICIQ-SF	International Consultation on Incontinence Questionnaire-Short Form
IDO	Idiopathic Detrusor Overactivity
IRB	Investigational Review Board
NDA	Neurogenic Detrusor Overactivity
OAB	Overactive Bladder
OABq-SF	Overactive Bladder Questionnaire-Short Form
PI	Principal Investigator
PTNS	Percutaneous Tibial Nerve Stimulation
PVR	Post Void Residual
QoL	Quality of Life
SNS	Sacral Neuromodulation
SUFU	Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction
U	Units
UA	Urinalysis
UCx	Urine Culture
UTI	Urinary Tract Infection
VAS	Visual Analog Scale

II. Background and Rationale

Overactive bladder (OAB) is a common condition with a prevalence ranging from 5.9% to 16.9% in the United States and has been found to increase with age.[1-4] OAB has a negative impact on health related quality of life (QoL),[5, 6] and OAB patients have more anxiety and depression than controls.[7, 8] Primary treatments for OAB include behavioral modifications, such as decreased caffeine intake and timed voiding, and pelvic floor physical therapy. Second line therapy includes anticholinergic medicine/beta-3 adrenoceptor agonists. Unfortunately, compliance and adherence to these medications decreases over time likely due to side effects and/or efficacy.[9-13] Per American Urological Association and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (AUA/SUFU) guidelines, onabotulinumtoxinA (BTX) is a third line recommendation for OAB along with percutaneous tibial nerve stimulation (PTNS) and sacral neuromodulation (SNS).[14]

The Food and Drug Administration (FDA) first gave BTX initial approval for use in 1989. BTX, however, was first described for use in the urinary bladder by Stohrer and colleagues in 1999.[15] It was FDA approved for use in neurogenic detrusor overactivity in 2011 and refractory idiopathic detrusor overactivity or overactive bladder in 2013. Since 1999 many studies have looked at the delivery and dosage of this neurotoxin into the bladder for OAB. In the beginning, patients were receiving BTX through as many as fifty injection sites, but after many studies confirmed similar efficacy, it is now common practice to inject BTX through ten injection sites.[16-19] Similarly, studies have looked at the appropriate dosage of BTX for OAB; the results of these studies have indicated 100 units(U) as the best dose for non-neurogenic patients with OAB.[20-22]

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BTX has transitioned over the years from a procedure conducted in the operating room to one that is commonly done in the clinic or physician office. Consequently, there has been continuing interest in reducing the number of injection sites further to make the technique more tolerable and more efficient. Preclinical studies in rats have shown similar effects of BTX between four and eight injection sites.[23] Additionally, Avallone et al recently published a pilot study which evaluated the use of one, two and three total injection sites (one for each 100 U). Their population included idiopathic detrusor overactivity (IDO) as well as neurogenic detrusor overactivity (NDO) patients. They found administering BTX via one to three sites had similar clinical efficacy and rates of adverse events compared to the established protocol for the respective groups.[24]

Due to these findings, we propose a randomized study where refractory OAB patients receive 100 U of BTX over either 3 or 10 injection sites. We will maintain the currently accepted dilution standard for BTX as there have not been studies specifically researching this factor yet. BTX will be reconstituted at a concentration of 10 U per 1 cc; 100 U will be reconstituted with 10 cc of injectable saline.

We have chosen three sites over one injection site specifically because an MRI study completed by Mehnert et al[25] reported, on average, 17.6% of injected BTX was found at the middle or lateral aspects outside of the bladder dome. There was, however, one patient who had contrast beyond the bladder base. Of note, this study had two arms: a 30-site group and a 10-site group with three neurogenic detrusor overactivity patients in each. The 30-site group had 300 U of BTX diluted in 27 cc of injectable saline plus 3 cc of gadopentetate (MRI contrast agent) while the 10-site group had 300 U of BTX diluted in 9 cc of injectable saline plus 1 cc of gadopentetate. Despite nearly 20% of the injected BTX being found outside of the bladder, coverage of the detrusor muscle itself was not significantly different between the two groups; at about 30% detrusor coverage, this was found to be sufficient enough to report similar success rates as reported in the literature.[25] Due to the findings in this study that 20% of the injection can be found outside of the bladder, we decided against a single injection and opted for three injection sites.

OAB is a prevalent condition affecting up to one of every 6 adults.[4] BTX is a well-established third line therapy for refractory OAB. Decreasing the number of injection sites may improve patient tolerability and satisfaction with this office-based procedure and potentially reduce the rates of adverse events (AEs) including hematuria and urinary tract infection (UTI).

Although a pilot study has been published regarding injection sites as few as one for 100 U of BTX, there has not been a randomized study comparing fewer injections sites to what is commonly practiced (ten injection sites). We hypothesize that a 3-site injection method is as effective as 10-site method and will lead to higher patient satisfaction.

III. Objectives and Endpoints

The primary aim of this study is to determine whether distributing 100 U of onabotulinumtoxinA over less injection sites (three) is just as effective as common practice (ten).

Our secondary aim is to assess whether less injection sites has fewer complications (UTI/ hematuria) and leads to better patient satisfaction and tolerability as this procedure is done in the office while the patient is awake.

We hypothesize that a 3-site injection method is as effective as a 10-site method and will lead to higher patient satisfaction. The primary outcome will be incontinence episodes per day assessed at 3 months after BTX injection. Secondary outcomes will include voiding symptom scores and voiding diary parameters as measured by the Overactive Bladder Questionnaire-Short Form (OABq-SF), International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF), Global Response Assessment (GRA), Visual Analog Scale (VAS) on the day of injection to assess for pain, satisfaction, and tolerability, and 3-day voiding diaries to be completed throughout the study.

IV. Methodology

Although a pilot study has been published regarding injection sites as few as one for 100 U of BTX, there has not been a randomized study comparing fewer injections sites to what is commonly practiced (ten injection sites).

Patients diagnosed with OAB and that have failed first and second line treatments will be presented with all third line therapies including BTX, SNS, and PTNS. Patients choosing BTX will be offered an opportunity to enroll in this study. If patients are already clinical responders and currently receiving BTX therapy, they are eligible for randomization if they choose to participate in the study. If they had prior BTX and were clinical non-responders they will not be eligible. Clinical non-responders are patients who previously reported no subjective improvement in their symptoms by 3 months after their injection. If a patient was an initial responder (with subjective improvement reported by the patient), and the effect has since worn off, the earliest they can receive re-injection will be 3 months after their initial injection. All repeat injections will be done at with a minimum of 3 months in between injections.

Consent to send out pre-screening activities may be done by telephone script with all elements of information sheet included. Participant agreement is consent to send pre-screening activities. Once the participant is present for enrollment visit, a formal consent will be performed for study participation. Informed consent will be obtained from all patients prior to conducting any study activities. Consented patients will complete the OAB-q SF, ICIQ-SF, 3-day voiding diary and enrollment questionnaire (demographics, medical history, concomitant medications, etc.) prior to study enrollment. A urinalysis (UA) will be collected at this visit as well and a urine culture (UCx) will be performed, if necessary. If the patient meets the eligibility criteria, they will be randomized (1:1) into the 3-injection site group or the 10-injection site group. We plan on performing a stratified randomization so the number of BTX naïve and previous BTX responder patients will be equivalent in both arms in order to minimize selection bias. Patients will be blinded to the number of injections they will receive. Adverse events and concomitant medications will be assessed at each follow-up visit. A diary will also be completed, collected and reviewed at each follow-up visit. GRA will also be gathered at each follow up visit. Visual Analog Scores will be gathered at the end of the injection visit to assess for patient satisfaction, pain, and tolerability.

Patients will be asked to remain off any oral anticholinergic or beta-3 agonist medications, PTNS therapy, or any neuromodulation throughout the entirety of the study.

Patients will follow up two weeks post-injection (±7days) for an office visit. OAB-q SF, GRA, ICIQ-SF, 3-day voiding diary, UA and post void residual (PVR) will be collected. If necessary, a UCx will be ordered for evaluation.

At 3, 6, 9, and 12 months post-injection (± 14 days), patients will return for follow-up appointments. OAB-q SF, GRA, ICIQ-SF, patient satisfaction, 3-day voiding diary, and UA will be collected. If necessary, a UCx will be ordered for evaluation. We will also assess for adverse events and concomitant medications at each of these visits. Specific adverse events we will be tracking include urinary retention (inability to void), elevated PVR of greater than 300 cc, UTI, excessive bleeding at injection sites that requires cautery, and systemic BTX effects (systemic weakness). If at any visit the patient is found to have a UTI, they will be prompted to repeat that visits questionnaires and 3-day diary at an unscheduled visit once the prescribed UTI treatment has been completed. At the unscheduled visit AEs will be reviewed and a clinical decision will be made by an investigator if UTI symptoms are still present after treatment completion. The unscheduled visit will occur at the urology research clinic.

If a repeat botox injection is given at the 3, 6, or 9 month visit, the subject will have a 2 week follow up visit identical to visit 3 in the schedule of events before continuing to be followed every 3 months.

While in-person visits are preferable, if the patient is unwilling or unable to attend a study visit (specifically visits 4-7) they will not be withdrawn from the study. In order to assess patient safety and provide continuing follow-up, the patient may be contacted by phone and/or mail. If necessary, study information may be collected by either or both of these methods; phone (current medications, AE assessment) and/or mail (questionnaires, voiding diary). If a patient requires a remote visit, they may complete at least one, but not all visits remotely.

Schedule of Research Activities

	Consent and Screening	Enrollment and Treatment	2 Weeks Post-BTX Visit (±7 days)	3 Months Post-BTX Visit[d] (± 14 days)	6 Months Post-BTX Visit[d] (± 14 days)	9 Months Post-BTX Visit[d] (± 14 days)	12 Months Post-BTX Visit (± 14 days)
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Consent	X						
Eligibility	X						
Demographics, Medical History	X						
OABq-SF ICIQ-SF	X		X	X	X	X	X
3-day Voiding Diary	X		X	X	X	X	X
Urinalysis, Urine Culture as needed	X	X	X	X	X	X	X
Pregnancy test before injection as needed[a]	X	X		X	X	X	
Post void residual (PVR)[b]			X				
BTX injection		X					
Repeat BTX				X	X	X	

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Injection[c]							
GRA			X	X	X	X	X
VAS		X		X[e]	X[e]	X[e]	
Concomitant Medications	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X

[a] If the patient has the potential to be pregnant (ie. pre-menopausal and/or no surgical history of hysterectomy/oophorectomy), a pregnancy test will be checked prior to all BTX injections.

[b] If the PVR is elevated at 2 week follow-up appointment, additional follow up for management of elevated PVR will be at the discretion of the provider (see below for definition and additional detail).

[c] Repeat injections will be offered at the clinician's discretion. Patients will be eligible for repeat injections 3 months after initial injection. Patients will be allowed to undergo repeat injections at a minimum of a 3 month interval. Injection will not be offered at the 12 month visit as this is the final study visit.

[d] If a patient is re-injected with Botox they will have a 2 week follow-up visit during which, time, the same activities as shown in visit 3 will be conducted.

[e] If patients request a repeat BTX injection, a VAS questionnaire will be performed post injection.

Injection Procedure

The injection procedure consists of injections of 100 U for IDO at 3 or 10 injection sites. The BTX will be reconstituted at a concentration of 10 U per 1 cc as is common practice. For example, a 100 U dose will be diluted with 10 cc of injectable saline. The diagram below shows the injection sites at the bladder base (just beyond the trigone). The procedure requires local lidocaine anesthesia only.

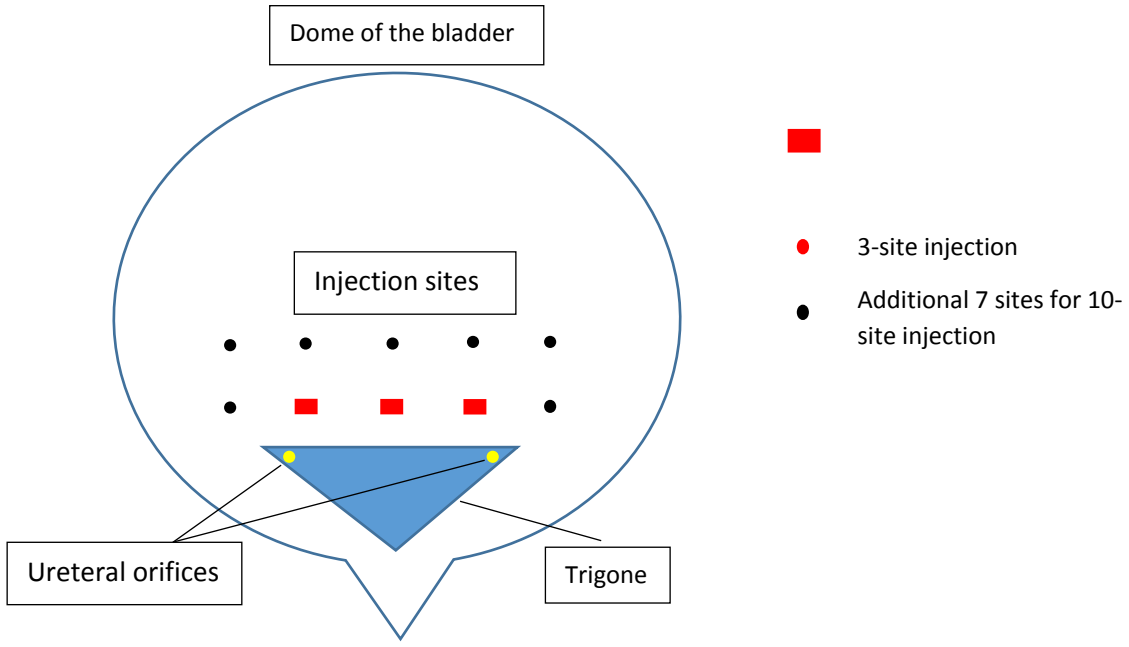

Figure 1. 3- and 10- site cystoscopic injection locations are outlined in the bladder.

Pre- and post-procedure antibiotics will be given at the discretion of the provider. After a negative urine analysis or if a patient has a positive dipstick (positive leukocyte esterase

and/or positive nitrites and/or positive blood) but is asymptomatic for a UTI, will proceed with Botox injections at the clinicians discretion. The patient's urethra will be prepped with betadine and 50 ml of 1% liquid lidocaine plain will be instilled, via catheter, into the patient's bladder and left for 10 minutes.

A flexible cystoscope will be used for the in-office procedure. This will be sterilized per standard office procedure between uses. A one-time use, Laborie injeTAK®, 23-gauge cystoscopic injection needle will be utilized as this is the needle used in both practices. The needle is retractable and can be adjusted to 0, 2, 3, 4, and 5 mm lengths. The needle will be extended out to 3 mm. Bladder wall thickness is dependent on the condition of the patient's bladder as well as degree of distention. Based on the literature, average bladder wall thickness on ultrasound of patients with OAB ranges from 4 to 6 mm.[26] This can of course vary with degree of distention. Based on these findings, and in conjunction with previously mentioned MRI findings of nearly 20% extravasation using a 4 mm needle depth[25], we opted for a 3 mm needle depth.

Additionally, a recent meta-analysis showed no difference in efficacy or safety according to depth of injection (suburothelial vs. intradetrusor).[27] Based on these findings, we will leave it up to the surgeon to decide between suburothelial or intradetrusor injections. This data, however, will be collected for analysis at the end of the study.

The patient will receive BTX injections according to the group to which they have been randomized. If the patient has been randomized into the 3 injection group, they will receive an additional 7 "sham injections" with the needle retracted (no break in the mucosa). We decided on this as a sham treatment instead of actually puncturing the mucosa without injecting BTX because the point of our study is also to assess patient satisfaction and tolerability as well as rates of adverse events (ie hematuria and UTI). In order to do this, we want to puncture the mucosa less (3 vs 10). For the 3 injection group, every 3rd injection will be an actual mucosal penetration and injection (for 3 total injections containing BTX) in order to keep the patient blinded as best as possible. The 3 BTX injections will still be placed in the location as outlined in the diagram (Figure 1). The other 7 injection's will be verbally emphasized by the clinician but will not have mucosal penetration with the needle. It has been our experience that patients have variable sensation with needle penetration, sometimes no or minimal sensation to a clear sensation of a needle poke. The provider will verbalize the injection number to the patient whether it is a true injection or not in order to keep a believable pace. All patients will be told "This is injection #1. This is injection #2. This is injection #3." and so forth. Care will also be taken to prevent the patient from seeing the syringe so they cannot guess the arm of the study to which they were randomized. All patients will think they are receiving ten injections. Post-injection, the patient will be evaluated for hemostasis. Cautery will be used if deemed necessary by the physician. If hemostasis is achieved, this will conclude the visit.

If at the 2 week follow-up the patient has an elevated post-void residual (PVR) <350cc and is symptomatic or if the patient has a PVR > 350 cc and is non-symptomatic, the patient may be placed on either clean intermittent catheterization (CIC), one time straight catheter with close follow-up or indwelling foley catheter. Management for elevated post void residual

(PVR) will be at the discretion of the provider. If the patient is a clinical non-responder by 3 months follow-up, subsequent management will be at the clinician's discretion. These patients will be followed, and data will be collected. We plan on conducting an intent to treat analysis which will identify any subject not assessed at 3 months after the first BTX injection as a treatment failure. However, patients who are clinical responders by 3 months and have return of symptoms will be eligible for retreatment. If patients undergo re-treatment, they will continue to receive the same number of injections they originally received. In other words, if they were originally randomized into the 3 injection arm, they will receive 3 injections at retreatment.

After any retreatment, patients will have a 2 Week Follow-up visit before continuing to be followed every 3 months. Findings of an elevated PVR will be addressed as stated above.

If the patient had systemic BTX effects the patient will not be offered repeat injections. If they have hematuria, UTI(s), or temporary urinary retention, they can be offered retreatment at the patient and clinician's discretion.

V. Risks and Benefits

Possible Risks of OnabotulinumtoxinA:

Side effects and discomforts that have been observed in patients who have received treatment with this study medication for their OAB symptoms include:

Most Frequent (occurring more than 10% of the time):

- weakness of the bladder muscle resulting in difficulty in urination or an inability to urinate or empty the bladder (urinary retention) for an extended period (less than a month in most cases, but could be longer)

Less Frequent (occurring from 1% to 10% of the time):

- constipation

Rare (occurring less than 1% of the time):

- generalized weakness

Possible Risks of Injection Procedure:

As with any injection, patients may experience local pain/soreness, bleeding, bruising, infection, and/or swelling. Some people feel faint or pass-out when being injected with medications.

The following side effects have been observed in patients who have received treatment with this study medication for their OAB symptoms:

Most Frequent (occurring more than 10% of the time):

- urinary tract infection

Less Frequent (occurring from 1% to 10% of the time):

- blood in the urine
- difficulty or painful urination

Rare (occurring less than 1% of the time)

- temporary bleeding at the injection site resulting in a blood clot in the bladder tissue
- urosepsis (an infection that occurs when urinary tract infection spreads to the bloodstream)

The following side effects have not been observed previously with study medication injections but could possibly happen:

Less Frequent (occurring from 1% to 10% of the time):
- permanent tissue damage from repeated injections
- accidental bladder wall puncture resulting in onabotulinumtoxinA introduction into abdominal space or near-by structures
- injury from the cystoscope resulting in temporary urethral swelling, urethral injury, blockage of urine flow, or overstretching of the bladder
- increased blood pressure
- headache
- decreased heart rate

Rare (occurring less than 1% of the time):
- local pain/soreness
- bleeding
- bruising
- infection
- swelling
- feeling faint or passing out when being injected

Possible Risks of Cystoscopy

Less Frequent (occurring more than 1% but less than 10% of the time):
- discomfort or pain
- cramps
- infection
- painful or difficult urination

Rare (occurring less than 1% of the time):
- bleeding (blood in urine)
- inability to pass urine after the procedure
- trauma
- urinary tract infection
- puncture of the bladder
- temporary swelling or injury to the urethra
- overstretching of the bladder
- a change in urinary frequency
- urgency in urination, including urgency resulting in episodes of urge incontinence

Risks of Antibiotic (Medicine to Prevent Infection)

Less Frequent (occurring more than 1% but less than 10% of the time):
- Diarrhea

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- Nausea and vomiting
- Stomach cramping

Rare (occurring less than 1% of the time):

- Headache
- Itching
- Rash
- Allergic reaction

There may be no direct benefit in taking part in this study. Symptoms of OAB may improve, but this cannot be guaranteed. Information gained from the results of this study may be of benefit to others in the future, with a similar medical condition.

VI. Eligibility Criteria

Inclusion criteria:

- Women and men ≥ 18 years of age
- Self-reported failed conservative care of behavioral modifications and/or oral medications for the treatment of OAB
- Average urinary frequency of ≥ 8 voids per day as recorded on initial 3-day voiding diary
- Self-reported bladder symptoms ≥ 3 months
- Discontinued antimuscarinics/beta-3 agonists for ≥ 2 weeks prior to study enrollment. May restart antimuscarinics/beta-3 agonists if indicated > 6 weeks after Botox injections.
- Previous onabotulinumA injection at least three months prior to study enrollment
- Capable of giving informed consent
- Capable and willing to follow all study-related procedures

Exclusion criteria:

- Pregnant or planning to become pregnant during study duration
- Diagnosis of neurogenic bladder with the exception of highly functioning stroke patients.
- If a patient has had a previous neuromodulation device placed, it will have to be turned off for 2 weeks for a washout period prior to enrollment and remain off throughout the study
- Previous non-responders to BTX therapy
- Known hypersensitivity to onabotulinumtoxinA
- Previous infection at onabotulinumtoxinA injection site
- Patient cannot be receiving PTNS therapy. If patient is receiving PTNS, they need to stop for 1 month prior to entering the study.
- Refusal to self-catheterize or have indwelling catheter in the event of urinary retention
- Use of investigational drug/device therapy within past 4 weeks
- Participation in any clinical investigation involving or impacting gynecologic, urinary or renal function within past 4 weeks
- Current or past history of any physical condition that, in the investigator's opinion, might put the subject at risk or interfere with study results interpretation

- Pelvic radiation treatment

VII. Data Analysis

Statistical Analysis

Primary Effectiveness

The primary efficacy endpoint is defined as at least a 50% reduction in number of urgency related incontinence episodes at 3 months. The number of urgency incontinent episodes per day is measured as the average of two, 3-day, consecutive bladder diaries. Patients shall be classified as treatment successes or treatment failures based on this criterion.

The primary hypothesis is that the proportion of patients who are treatment successes with BTX-3 is non-inferior with a margin of 15% to that with BTX-10 at 3 months.

H_o: $p_{BTX\text{-}3} \leq p_{BTX\text{-}10} - 0.15$ vs H_a: $p_{BTX\text{-}3} > p_{BTX\text{-}10} - 0.15$

In the hypothesis equations, 0.15 is the clinical equivalence margin for the non-inferiority test of this hypothesis.

Sample Size and Power Calculation

One hundred seventy-eight (178 patients will be randomized in this study, 89 per group to achieve 80% power to detect a non-inferiority margin difference between the group proportions of 0.15. The reference group (BTX-10) proportion is 0.85. The treatment group proportion (BTX-3) is assumed to be larger than 0.70 under the null hypothesis of inferiority. The power was computed for the case when the actual treatment group proportion is 0.85, that is both BTX-10 and BTX-3 had the same response rate of 0.85. The test statistic used is the one-sided Z test with a Type I error rate of 0.025.

Table Non Inferiority Sample size; *Margin of 0.15 and expected delta=0*

Power	N1	N2	N	Reference (BTX-10) Responder Rate	BTX-3 Responder Rate|H0	BTX-3 Responder Rate|Ha
0.8	147	147	294	0.7	0.55	0.7
0.85	168	168	336	0.7	0.55	0.7
0.9	197	197	394	0.7	0.55	0.7
0.8	131	131	262	0.75	0.6	0.75
0.85	150	150	300	0.75	0.6	0.75
0.9	176	176	352	0.75	0.6	0.75
0.8	112	112	224	0.8	0.65	0.8
0.85	128	128	256	0.8	0.65	0.8
0.9	150	150	300	0.8	0.65	0.8

Table Non Inferiority Sample size; *Margin of 0.15 and expected delta=0*

Power	N1	N2	N	Reference (BTX-10) Responder Rate	BTX-3 Responder Rate|H0	BTX-3 Responder Rate|Ha
0.8	**89**	**89**	**178**	**0.85**	**0.7**	**0.85**
0.85	102	102	204	0.85	0.7	0.85
0.9	120	120	240	0.85	0.7	0.85
0.8	63	63	126	0.9	0.75	0.9
0.85	72	72	144	0.9	0.75	0.9
0.9	85	85	170	0.9	0.75	0.9

At 3 months, the percentage of patients who are successfully treated will be computed for each treatment group. Patients who exit the study early citing reasons of inadequate urge or incontinence reduction will be included in this analysis as *treatment failures*. Treatment-failure patients are otherwise known as *non-responders*.

The success rate in the BTX-3 group will be compared to that in the BTX-10 group using a non-inferiority at $\alpha = 0.025$ and $\delta = .15$ as shown earlier in this protocol.

Data analyses

A biostatistician will perform all statistical analyses using SAS or similar statistical software. Descriptive statistics will be calculated. A completer analysis will be conducted for those who finish the study per protocol. The primary endpoint will be assessed comparing incontinence episodes per day at 3 months after BTX injection. This comparison will also be made for all other visits using t-tests or chi-square tests, as appropriate.

Secondary endpoints will include adverse events and comparisons between 3-site and 10-site groups looking at the GRA responses between 3-site and 10-site groups at 3 months (± 14 days) post injection, 3-day voiding diary and OABq-SF and ICIQ-SF at 3 months (± 14 days) post-injection. We will also compare post-injection VAS scores to assess for tolerability, satisfaction, and pain. Changes from baseline will also be analyzed. This comparison will also be made for all other visits using appropriate statistical tests.

In addition to a completer analysis, we also plan on conducting an intent to treat analyses which will identify any subject not assessed at 3 months after the first BTX injection as a treatment failure. In order to assess for all possible situations, 4 different scenarios will be run: 1) All dropouts will be considered non-responders for both groups 2) All dropouts will be considered responders for both groups, 3) Dropouts in the BTX 10 group will be considered responders and those in the BTX 3 group, non-responders, and 4) Dropouts in the BTX 10 group will be considered non-responders while those in the BTX 3 group, responders.

VIII. Data Safety Monitoring Plan

Ongoing safety monitoring will be performed by the study staff, including the Principal Investigator (PI) and co-investigators. The PI will have ultimate responsibility of assuring patient safety. Safety issues will also be addressed in the annual reports to Beaumont's Investigational Review Board (IRB).

Additional data safety monitoring procedures include:

- Research Administration's Clinical Research Quality and Process Improvement Program (CRQIP) will perform in-house monitoring of the first patient enrolled after the completion of visit 1

- An audit of the study records after the first 10 patients are enrolled and at the half way point of enrollment by Urology Research Nurse that is not directly involved with the research study. This will be done to ensure the safety of patients and lack of significant adverse effects. Additional auditing may occur, as needed.

- Throughout the study all adverse effects will be reported to the research nurse and then to the PI at the time of the event. Adverse events, serious adverse events, and unanticipated problems not listed in the risks section of this protocol will be reported per IRB guidelines.

Once 25 patients have been randomized to each arm, we will assess the efficacy/futility of BTX injections based on the 3-month follow-up visit data.

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