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TITLE: A Double-Blind, Randomized Study of Safety and Efficacy of OnabotulinumtoxinA (OnaBoNT-A) versus Oral Oxybutynin in SCI Patients with NDO (11-09-10-04)

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14. ABSTRACT The purpose is to evaluate the safety and efficacy of 200 U OnaBoNT-A injected into the detrusor versus oral oxybutynin for the treatment of urinary incontinence (UI) caused by neurogenic detrusor overactivity (NDO) in spinal cord injured volunteers; and (2) To determine the potential role of urine biomarkers as patient selection and surrogate endpoints of treatment outcome predictors. Thirty-six patients will be randomized to two treatment groups. The first patient was enrolled to the study at The Institute of Rehabilitation and Research (TIRR) on June 17, 2016. A total of thirteen patients have been consented to date at TIRR. Three have completed the study. Three are continuing on protocol with each having been injected with the study drug. Enrollment is continuing. The study was closed at the Michael E. DeBakey Veterans Affairs Medical Center – Houston in July 2016 due to lack of accrual.					
15. SUBJECT TERMS Botulinum Toxin, Oxybutynin, Overactive Bladder, Spinal Cord Injury, Urinary Incontinence, Nerve Growth Factor, Urine Biomarkers					
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Annual Report for W81XWH-12-1-0549 SC110198:

A Double-Blind, Randomized Study of Safety and Efficacy of OnabotulinumtoxinA (OnaBoNT-A) versus Oral Oxybutynin in SCI Patients with NDO (11-09-10-04)

INTRODUCTION

This is a Phase 3B, double-blind, randomized, placebo-controlled, parallel-group study to assess the safety and efficacy of onaBoNT-A or 10 mg twice a day of oral oxybutynin hydrochloride ER in 36 spinal cord injured patients who visit TIRR Memorial Hermann in Houston, TX and are diagnosed with neurogenic detrusor overactivity. Volunteers will include both males and females who are 18 to 80 years of age. There are no eligibility restrictions as to race or ethnicity.

Previously, the study was also open to enrollment at the Michael E. DeBakey Veterans Affairs Medical Center – Houston. It was closed at the BCM IRB on July 25, 2016 due to lack of accrual.

KEYWORDS

Botulinum Toxin, Oxybutynin, Overactive Bladder, Spinal Cord Injury, Urinary Incontinence, Nerve Growth Factor, Urine Biomarkers

OVERALL PROJECT SUMMARY

The major goals of this project are to evaluate the safety and efficacy of 200 U OnaBoNT-A injected into the detrusor versus oral oxybutynin for the treatment of urinary incontinence (UI) caused by neurogenic detrusor overactivity (NDO) in spinal cord injured volunteers and to determine the potential role of urine biomarkers as patient selection and surrogate endpoints of treatment outcome predictors. Thirty-six patients will be randomized to two treatment groups.

Four subjects were enrolled and reported in the January 2017 Quarterly Report. Five subjects were enrolled and reported in the April 2017 Quarterly Report. Two subjects were enrolled and reported in the July 2017 Quarterly Report. Two subjects were enrolled in this 4th Quarter. Three subjects have completed the study. In the past year, 1,013 charts have been reviewed and 53 patients were referred by the staff.

The protocol has undergone three revisions in the past year.

Protocol v. 3/15/17:

Exclusion Criteria

Section 7.2, page 18

Added: PSA age to be checked is on male patients 50 years or older, unless has a family history of prostate cancer or is of African American decent then PSA age to be checked is at age 40 years old.

Section 10.1, page 20

Added: PSA age to be checked is on male patients 50 years or older, unless has a family history of prostate cancer or is of African American decent then PSA age to be checked is at age 40 years old.

Section 10.2.1, page 21

Was: Serum Pregnancy test (for females only)

Now: Urine Pregnancy test (for females only). If positive, a serum pregnancy test will be conducted to confirm.

Section 10.3.2, page 23

Was: Serum Pregnancy test (for females only)

Now: Urine Pregnancy test (for females only). If positive, a serum pregnancy test will be conducted to confirm.

Risk Management and Emergency Response

Section 16.2.1

Was: Serum pregnancy test for female volunteers of childbearing potential at screening, qualification for re-treatment, and study exit

Now: Serum pregnancy test for female volunteers of childbearing potential at screening, qualification for re-treatment if urine pregnancy is positive, and study exit

Was: Serum pregnancy test for female volunteers of childbearing potential on day of treatment (prior to each treatment). If positive, a serum pregnancy test will be conducted to confirm.

Now: Urine pregnancy test for female volunteers of childbearing potential on day of treatment (prior to each treatment). If positive, a serum pregnancy test will be conducted to confirm.

Protocol v.5/11/17

Randomization

Section 6, page 16

Added: Volunteers will be encouraged to washout of medication for 14 days. If they choose to remain on medicine, they will stay on same dose for duration of the study

Inclusion Criteria

Section 7.1, page 16

Revised lower age limit to 15

Exclusion Criteria

Section 7.2, page 18

Deleted: #6.

Informed Consent Process

Section 9, page 19

Added: For children ages 15 through 17 years old, assent will be obtained by adding "If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this, you also note that your child understands and agrees to take part in this study according to his or her understanding." to the adult consent form.

Risk/Benefits Assessment

Section 16.1.2, page 29

Added: If side effects occur, they will be managed as effectively as possible.

HPRO Report: Protocol v.5/11/17 required a HPRO amendment submission.

12Jul2017 E-mail to HPRO contact
20Jul2017 E-mail confirmation of accept by HPRO contact
26Jul2017 E-mail to HPRO requesting expected time of approval
03Aug2017 E-mail to HPRO requesting expected time of approval
03Aug2017 E-mail from HPRO requesting:
– justification of enrolling minors
– Justification for signed assent by subjects capable
Amendment application submitted to IRB
03Aug2017 Email to HPRO with responses
08 Aug2017 Email from HPRO indicating that information was sent to approval authority
10Aug2017 Email from HPRO indicating that a deeper review is needed due to child placebo
31Aug2017 Email form HPRO requesting additional documentation
01Sep2017 E-mail documents to HPRO
05Sep2017 E-mailed HPRO with status report request
05Sep2017 Email from HPRO requesting IRB approval to add TIRR as a study site.
Indicated that the HPRO file was in 'a mess...So many people have left and can't see to find documents"
05Sep2017 E-mailed requested documents to HPRO
20Sep2017 E-mailed HPRO with status report request
04Oct2017 E-mailed HPRO with status report request
09Oct2017 Left voice-mail for HPRO

It is noted that patients are not being enrolled to protocol v.5/11/17.

Protocol v.6/20/17

Inclusion Criteria

Section 7.1, page 16

Revised lower weight limit to 90 pounds. It is noted that the consent form doesn't require revision.

IRB actions since the 2016 annual report submission include the following:

- 17Mar2017 IRB annual renewal submission
- 31Mar2017 IRB renewal approval
- 14Apr2017 Amendment submission for Protocol v. 3/15/17
- 14Apr2017 IRB amendment approval
- 10May2017 Amendment submission for Protocol v. 5/11/17
- 19Jun2017 IRB amendment approval

- 27Jun2017 Amendment submission for Protocol v. 6/20/17
- 11Jul2017 IRB amendment approval

KEY RESEARCH ACCOMPLISHMENTS: Nothing to report

CONCLUSIONS

We are encouraged by the amounts of patients referred and remain hopeful that we can meet enrollment goals. A No Cost Extension has been requested in order to complete enrollment.

PUBLICATIONS ABSTRACTS AND PRESENTATIONS: None

INVENTIONS, PATENTS AND LICENSES: None

REPORTABLE OUTCOMES: None

OTHER ACHIEVEMENTS: None

REFERENCES: None

ATTACHMENTS:

- Protocol v.3/15/17
 - Changes document
 - Full protocol
- Protocol v.5/11/17
 - Changes document
 - Full protocol
- Protocol v.6/20/17
 - Changes document
 - Full protocol
- IRB approved documents
 - Annual renewal 3/31/17
 - Protocol v.3/15/17
 - Protocol v.5/11/17
 - Protocol v.6/20/17

H-34972: A Multicenter, Double-Blind, Randomized Study of the Safety and Efficacy of OnabotulinumtoxinA (ONAb_oNT-A) versus Oral Oxybutynin in Spinal Cord Injured Patients with Neurogenic Detrusor Overactivity (Protocol Number 11-09-10-04)

Protocol Changes from 8/20/2016 to 3/15/17

Study Procedures:

Exclusion Criteria

Section 7.2, page 18

#8. Added: PSA age to be checked is on male patients 50 years or older, unless has a family history of prostate cancer or is of African American decent then PSA age to be checked is at age 40 years old.

Section 10.1, page 20

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Now: Urine pregnancy test for female volunteers of childbearing potential on day of treatment (prior to each treatment). If positive, a serum pregnancy test will be conducted to confirm.

A Double-Blind, Randomized Study of the Safety and Efficacy of OnabotulinumtoxinA (ONAbNT-A) versus Oral Oxybutynin in Spinal Cord Injured Patients with Neurogenic Detrusor Overactivity (Protocol Number 11-09-10-04)

Protocol Version: March 15, 2017

PHASE 3B

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KEYWORDS: Botulinum Toxin, Oxybutynin, Overactive Bladder, Spinal Cord Injury, Urinary Incontinence, Nerve Growth Factor, Urine Biomarkers

BCM IRB NUMBER: H-34972 (TIRR Memorial Hermann)

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1. BACKGROUND

1.1 Pathophysiology of Neurogenic Bladder (NGB) due to Spinal Cord Injury (SCI)

Overactive bladder is a condition resulting from disruption of the normal micturition process. It is a syndrome complex characterized by urinary urgency and frequency that may or may not be accompanied by incontinence. Incontinence is due to involuntary contraction of the bladder smooth muscle during bladder filling (detrusor overactivity). [Mills et al, 2000] Neurological disease involving the spinal cord can result in incontinence secondary to a loss of inhibitory input from the micturition center and from interruption of the spinobulbospinal pathways which normally control bladder behavior. The result, demonstrable on urodynamic evaluation, is abnormal involuntary detrusor contractions, often leading to incontinence. In addition, such patients frequently also suffer from urethral sphincters that are unable to relax prior to micturition in a coordinated fashion (i.e. detrusor-sphincter dyssynergia). This lack of coordinated activity can result not only in incontinence but also in vesico-ureteric reflux and/or high storage and voiding pressures which, if left untreated, can lead to potential renal damage. [Foley et al, 1997]

1.2. Epidemiology and Burden of SCI induced NGB

Approximately 10,000 SCIs occur each year, most of which occur in males (80%) [De Vivo et al, 1992]. Many of these patients develop neurogenic bladder dysfunction (NGB) characterized by overactivity of the detrusor muscle, termed neurogenic detrusor overactivity (NDO) or the older term detrusor hyperreflexia (DH). Spinal cord injured patients can also develop detrusor external sphincter dyssynergia (DESD), an abnormal/uncoordinated response of the sphincter to bladder contraction. A combination of these factors can lead to *long-term complications in up to 50% of patients* [Kaplan et al, 1991; McGuire 1979; Yalla et al, 1977]. These complications include hydronephrosis, autonomic dysreflexia, vesicoureteral reflux, nephrolithiasis, sepsis, renal insufficiency or failure and even death. SCI patients often suffer from urinary incontinence which can lead to adverse events such as urinary tract infections and decubitus ulcers, in addition to creating a large care burden for family members or healthcare providers and significantly impairing the veteran's quality of life. Clearly, bladder problems related to SCI have a negative impact not only on patients' physical condition, but also on their emotional and social well-being. Low self-esteem resulting from urinary incontinence can reduce social interaction, depress sexual desire, and interfere with productivity at work, in school, or during rehabilitation of the veteran's primary neurological disease.

1.3. Current Treatment of NGB is Inadequate

Common pharmacologic treatments to reduce bladder contractility include anticholinergics, antispasmodics and tricyclic antidepressants. However, these therapies have limited efficacy and are associated with a high incidence of side effects including dry mouth, constipation and blurred vision [Ouslander, 2004]. A large randomized trial comparing propiverine to oxybutynin in SCI patients found that oxybutynin only reduced daily incontinence episodes by 39%. [Stohrer et al, 2007]. Furthermore, anticholinergic adverse effects were observed in 78% of oxybutynin treated patients in parallel with the limited benefit of the drug in reducing bladder related incontinence. In fact, a large epidemiological study of oral antimuscarinic drug use among NGB patients found that 38% stop therapy within one year of initiation of therapy. [Manack et al, 2011]

Although a large proportion of NGB patients are inadequately treated with standard front-line therapy with oral anticholinergics, up until recently, the only options available to patients who do not respond to or discontinue anticholinergic therapy are invasive procedures such as implantable devices to chronically stimulate the sacral nerve (i.e. limited studies showing utility in NGB patients) or surgical bladder augmentation (i.e. where intestine is harvested and sewn onto the bladder). While these procedures may be effective for some patients, they are highly invasive, expensive, do not necessarily guarantee continence, and may have long term complications [Bosch and Groen, 1998; Bosch, 1998].

1.4. OnabotulinumtoxinA (ONAbNT-A) as an Alternative Treatment of Refractory NGB

Botulinum toxin is a neurotoxin that acts by inhibiting neurotransmitter release from nerve endings. It is commonly used to treat conditions of skeletal muscle spasticity (i.e. cervical dystonia, etc.). In contrast to muscarinic antagonists whose primary beneficial effects are mediated by inhibiting parasympathetic mediated cholinergic transmission to the bladder, ONAbNT-A's denervating effects are widespread. In fact, ONAbNT-A has been shown to inhibit the release of multiple neurotransmitters (i.e. acetylcholine, ATP, norepinephrine) and growth factors (i.e. nerve growth factor, NGF) that depend on SNARE (i.e. soluble N-ethylmaleimide-sensitive factor attachment protein (SNAP) receptor) mediated release from nerve endings. [Abdel-Meguid, 2010] The use of ONAbNT-A in the urinary bladder was first described by Schurch and colleagues who demonstrated a significant increase in mean maximum bladder capacity (296ml to 480ml, $p < 0.016$) and a significant decrease in mean maximum detrusor voiding pressure (65 to 35cm H₂O, $p < 0.016$) in 21 patients with NDO that were injected with ONAbNT-A. [Schurch et al, 2000] A strong impetus driving industry sponsored clinical trials examining the effects of ONAbNT-A on NDO was provided by the first randomized, placebo-controlled trial examining the effects of two doses of ONAbNT-A (i.e. 200 or 300 units) versus saline injection on various parameters including urodynamic measurements and urinary incontinence episodes in patients with refractory NGB resulting from multiple sclerosis (i.e. MS) or SCI. [Schurch et al, 2005] Significant decreases in incontinent episodes (i.e. approximately 50%), significant increases in maximal cystometric capacity (i.e. approximately 170-215ml), and significant improvements in quality of life scores were demonstrated in both ONAbNT-A treatment groups compared to controls. Beneficial effects lasted the duration of the study (i.e. 6 months).

A second double-blind, randomized, placebo controlled study compared the effects of ONAbNT-A (300 U) in 57 patients with urinary incontinence resulting from MS or SCI. At 6 weeks following treatment, ONAbNT-A treated patients demonstrated a 57% reduction in daily incontinence episodes compared to no change in placebo treated patients. [Herschorn et al, 2011] Most recently, a Phase 3 double-blind, placebo-controlled, parallel group study compared the effect of two doses of ONAbNT-A (i.e. 200 U and 300 U) to placebo in 416 patients with urinary incontinence and NDO resulting from multiple sclerosis or SCI and not adequately managed with antimuscarinic medication. At 6 week follow-up, 200 U of ONAbNT-A reduced weekly urinary incontinence episodes by 69%, a significantly greater response than placebo treatment (i.e. 29%). [Ginsberg et al, 2011]

The preceding three randomized studies demonstrate that ONAbNT-A is more effective than placebo for improving the symptoms and signs of NDO, as measured by the reduction in episodes of urinary incontinence as well as improvements in urodynamic parameters. However, in each study **patients were allowed to remain on anticholinergic treatment throughout the duration of the study** so the absolute benefit of ONAbNT-A treatment cannot be assessed.

Moreover, although patients in each study were determined to be refractory to antimuscarinic treatment, the relative effectiveness of antimuscarinic medication versus ONAboNT-A in patients SCI patients suffering from urinary incontinence can only be determined through a randomized, controlled, trial comparing single treatment with either agent.

Finally, prior randomized trials have all excluded bladder trigone injections for fear of inducing vesicoureteral reflux. Studies have disproven this theory and, in fact, mounting evidence suggests that the bladder trigone is an ideal target for ONAboNT-A injections. [Smith et al, 2005; Abdel-Meguid, 2010] For starters, the bladder trigone is densely innervated and contains an abundant concentration of the high-affinity binding site for ONAboNT-A, SV2. [Coelho et al, 2010] Moreover, a recent randomized comparative trial between trigone and non-trigone bladder injection paradigms in patients with SCI induced NDO found that including trigone injections led to significantly greater improvements in urinary incontinence. [Abdel-Meguid, 2010] These findings parallel Dr. Smith and Dr. Chancellor's 14 year personal experience utilizing bladder trigone injections with ONAboNT-A. [Smith et al, 2005]

1.4.1 Use of ONAboNT-A to Treat SCI NGB Patients

We recently reviewed our results using ONAboNT-A in a high-risk population of SCI patients with NGB and decreased bladder compliance. Loss of detrusor compliance creates high urine storage pressure in the bladder with consequent risks to renal function. Data were collected from 24 patients with urinary incontinence secondary to SCI, all of whom underwent intradetrusor injection of ONAboNT-A at The Institute for Rehabilitation and Research (TIRR). [Mengheang et al, 2011] Each patient underwent injection of 300 units of ONAboNT-A, with the exception of one patient who received 100 units.

A total of 24 patients with incontinence of neurogenic origin were included in this study. Mean patient age was 33 years (range 15 to 65), and mean time since SCI was 8.5 years (range 7 months to 24 years). Of the 24 patients, 11 had cervical SCI, 8 had thoracic SCI and 2 had lumbar SCI; the other three patients suffered from transverse myelitis, spinal cord malacia, and cerebral palsy.

Overall, there was significant improvement in urodynamic parameters after ONAboNT-A injection (Table 1).

	Baseline	Follow-up	P value
Compliance (ml/cm H ₂ O)	14 ± 2	29 ± 5	0.002
Maximum cystometric capacity (mL)	322 ± 32	421 ± 33	0.008
Maximum det/ves pressure (cm H ₂ O)	59 ± 4	36 ± 5	<0.001
Reflex detrusor volume (mL)	155 ± 22	187 ± 33	0.37

Table 1. Urodynamic parameters at baseline and follow-up after ONAboNT-A injection

Notably, 22 (92%) of the 24 patients had low baseline compliance, defined as <20 ml/cm H₂O (mean 14 ± 2ml/cm H₂O). In this subset of 22 patients, baseline compliance increased 260% post-treatment, from a mean of 11.2 ± 1 to 29.2 ± 5 ml/cm H₂O, p=0.001 (Figure 2). Seventeen patients (77%) with low baseline compliance had an increase in compliance on follow-up urodynamics.

Furthermore, 18 of the 24 patients had an elevated maximum detrusor pressure (MDP) > 40 cm H₂O with reduction of MDP into the normal range in 9/18 (50%) after ONAboNT-A therapy. Overall, the mean MDP decreased from 59 ± 4 to 36 ± 5 cm H₂O.

Figure 2: A subset of 22 patients with incontinence of neurogenic origin responded to intradetrusor injection of ONAboNT-A with a 260% post-treatment increase of baseline compliance from 11.2 ± 1 to 29.2 ± 5 ml/cm H₂O, p=0.001

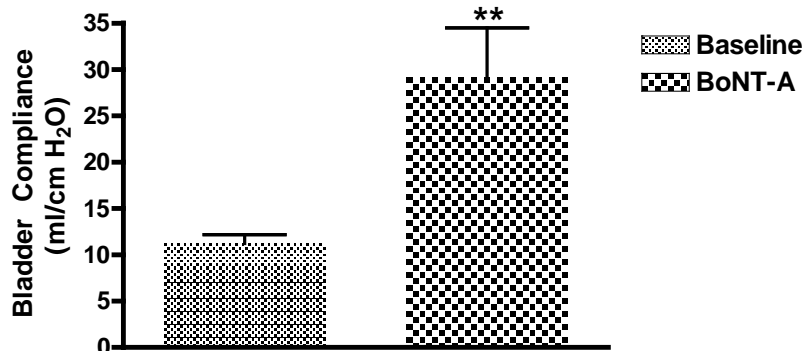


Figure 2. Bladder Compliance

Detrusor overactivity was documented in twenty-three of the 24 patients (96%) during urodynamic study (i.e. documented occurrence of an uninhibited contraction during bladder filling). Post-injection, only 11 (46%) of the 24 patients had uninhibited contractions on urodynamics. There was an increase in reflex detrusor volume on follow-up urodynamics, but it was not statistically significant.

Favorable clinical response was defined as a decrease in frequency of catheterization and/or absence of incontinence episodes. Eighteen of 24 patients (75%) reported a favorable clinical response as defined above. Of the 12 patients with low baseline compliance that experienced improvement in the normal range, 11 (92%) had a favorable clinical response.

1.4.2 Results

In summary, ONAboNT-A bladder injection can significantly improve objective and subjective parameters in SCI patients with high-risk bladders (i.e. decreased bladder compliance). In addition to prior clinical publications between Drs. Smith and Chancellor, [Smith et al, 2005] this data establishes these investigators as clinical experts in the application of ONAboNT-A to patients with urinary incontinence and NGB.

1.5. Urinary Biomarkers in Bladder Dysfunction

Existing therapeutic outcome measures for NGB patients heavily rely on subjective impressions of patients leading to high heterogeneity in clinical response to neuromodulation achieved either by pharmacological or physical means. In the studies described for Aim 2, we will test the following hypothesis to substitute a response variable continuous in nature (i.e. urinary biomarkers) in addition to subjective clinical outcome (i.e. change in urinary incontinence episodes). Nerve growth factor (NGF) is a potent neuronal growth factor with nociceptive and inflammatory properties recently shown to be of importance in bladder pathology. NGF is a

target organ derived growth factor that is produced by most organs lining the upper and lower urinary tract following pathologic insult. [Yoshimura, et al, 2006] NGF is known for neuroimmune interactions. NGF and its receptors may also amplify other immunoinflammatory and neuronal pathways contributing to bladder inflammation and leading to symptoms associated with NGB. We have previously demonstrated that urine NGF levels are elevated in various conditions of bladder dysfunction (i.e. interstitial cystitis, NDO) and can be reduced following bladder injection with ONAboNT-A. [Liu et al, 2009a; Liu et al, 2009b] Taken together, our preliminary data indicate that activation of the NGF and a network of chemokines represents a pivotal final pathway that can be used to construct a biomarker panel for analyzing NGB patients and assessing their treatment response to ONAboNT-A or oxybutynin.

Our hypothesis is that immune and neuronal mechanisms integrate to produce neuroimmune responses as an adaptive mechanism responding to SCI. A dense network of sensory nerve fibers is strategically placed just below the bladder epithelial surface so that any change in the urothelial environment may stimulate the release of proinflammatory neuropeptides by chemokines. [Gabella, 1999; Qin et al, 2005] Chemokines are chemotactic cytokines that constitute a large family of secretory proteins with a molecular weight of 7-10 Kd that are expressed by leukocytes and resident tissue cells.[Mortier et al, 2008] Chemokines exert their effect by interacting with G protein-coupled receptors present on glycosaminoglycans that are linked to endothelial cell layers. [Mortier et al, 2008] Recent studies have shown that chemokines may represent a group of neuromodulatory agents that can alter sensory processing in bladder. [Torrence et al, 2007; Yuridullah et al, 2006] Statistics favor that a panel of independent urinary markers composed of NGF and chemokines will be better than sole reliance on a single urine marker as a surrogate of efficacy of ONAboNT-A and oxybutynin treatment.

Studies have shown that cytokines/chemokines and chemokine receptors are not uniquely restricted to inflammation, but are also responsible for autocrine, paracrine and endocrine signaling by non-immune cells in the bladder such as urothelium and detrusor muscle cells. [Bouchelouche et al, 2004; Bouchelouche et al, 2006] Apart from infiltrated mononuclear cells, recent studies demonstrate that bladder inflammation can be amplified by the resident cells themselves in urothelium through the release of chemoattractants for various inflammatory cells. [Billips et al, 2007; Apostolidis et al, 2008; Schwentner et al, 2008] Previous pre-clinical studies in our lab have already shown that inflammatory signaling is reflected by levels of cytokines in biological fluids interacting with inflamed tissue [Tyagi et al, 2009b]. One of the crucial host defense responses is neutrophil migration to injured urothelium that involves a series of complex interactions with molecules in the lamina propria and at the epithelial barrier. [Godaly et al, 2001] The proteins measured in the urine of NGB like chemokine monocyte chemoattractant protein (MCP-1) and NGF have an established biological role in sensitizing afferents and producing symptoms associated with NDO. [Bhangoo et al, 2007] MCP-1 has also been shown to increase afferent excitability by sensitization of TRPV1 receptor on afferents and the mechanosensitive variant TRPA1 receptors [Jung et al, 2008]. The elevated urinary MCP-1 levels in patients with NGB may be responsible for exacerbation of symptoms by increasing afferent nerve excitability through modulation of TRPV1. The relationship of elevated MCP-1 with symptoms can also be explained by the dose dependent inhibition of GABAergic neurons by MCP-1. [Gosselin et al, 2005; Melik-Parsadaniantz and Rostene, 2008] GABAergic transmission is inherently inhibitory in nature and is likely to attenuate nociceptive transmission. [Miyazato et al 2008]

Urinary proteomics is an attractive option for clinical use, as urine is an ideal source for the discovery of noninvasive biomarkers for human diseases. Therefore, urine presents a rich

source of information for bladder diseases. Disease induced changes in urinary proteome can be traced to overexpression of proteins or abnormal shedding from urothelium into urine. [Tyagi et al, 2009a] Chemokines are subdivided into 4 families (CXC, CC, C and CX₃C) based on the relative position and number of conserved N-terminal cysteine residues as well as the absence (CC) or presence of intervening amino acid(s) between the cysteine residues (CXC). The CC and CXC family have more than one of its members that are implicated in inflammatory pathways.

Many studies have examined the urine as a possible source for biomarkers of urogenital disease because urine is in direct contact with the bladder and prostate and the molecular composition of urine can reflect biochemical and pathophysiological changes in the those organs. [Erickson et al, 2002]

Most of the biomarkers currently used in the clinic have emerged from targeted analysis of candidate biomarkers using immunoassays. [Pirtskalaishvili et al, 1999; Kronborg et al, 2007]] By focusing on a limited number of candidate biomarker proteins, assay technologies providing higher sensitivity and dynamic range such as Luminex can be used. Multiplexed immunoassays (i.e. Luminex) have allowed the measurement of biomarkers associated with bladder dysfunction with very low concentrations in urine that could not be measured for full patient cohorts with conventional immunoassays. In the proposed study, urine levels of chemokines and growth factors will be measured by multiplexed immunoassay panel and normalized by urinary creatinine levels.

The best-established microsphere assay system is the Luminex xMap system (Luminex Corp., Austin, TX), incorporating proven time tested technologies: bioassays, solution phase microspheres, and flow cytometry. [Tyagi et al, 2009a] The antibody specificity of multiplex immunoassays offers simultaneous analysis of a set of markers that can form a fingerprint of the patient responding to treatment with improved sensitivity and specificity. Sensitivity and specificity of biomarkers have been found to be potentiated by use of immunoassay panels which include chemokines, cytokines and angiogenic factors. The sandwich format utilized in the bead based assay as in traditional ELISA not only provides higher-specificity but also minimizes cross-reactivity with other urinary proteins.

1.5.1 Utility of Urinary Biomarkers in Bladder Dysfunction

Studies have shown that cytokines and chemokines responsible for autocrine, paracrine and endocrine signaling are also released by non-immune cells in the bladder such as urothelium and detrusor cells. [Bouchelouche et al, 2004; Bouchelouche et al, 2006a; Bouchelouche et al, 2006b] The urinary bladder relies on a broad array of cytokines, chemokines and growth factors to effect biochemical changes within its organ in response to disease and therapeutic intervention. But not all these chemokines/cytokines and growth factors can serve as urinary biomarkers or surrogates of treatment response as they have to fulfill the key requirement of being present in detectable amounts in urine that can be assayed using standard methods.

For example, although tumor necrosis factor (i.e. TNF) - α is the initiator of the inflammation process in the bladder, it is unlikely to serve as a urine marker for bladder inflammation [Billips et al, 2007; Bouchelouche et al, 2006a], because of its very small amount released into the urine. [Sadeghi et al, 2005] It is quite possible that released TNF- α binds with receptors in surrounding tissue such that only trace amounts are leaked into the urine. Thus, the release of cytokines and other inflammatory mediators into the urine is critical for their utility to serve as a biomarker. With the availability of reliable analysis methods based on immunoassays such as

ELISA, numerous studies have used cytokines as biomarkers in the diagnosis and prognosis for a host of diseases. [Parekattil et al, 2003; Parikh et al, 2006; Rovin et al, 2005; Segerer and Nelson, 2005; Mehta, 2006]

In contrast to urine levels of TNF- α in NGB patients, the detectable amount of NGF in the same patients combined with its known role in neuroimmune interactions makes NGF an ideal candidate for a urinary biomarker. A role for NGF in the development of UTI is not well elucidated and the aims of our preliminary study were to investigate the secreted levels of NGF in urine from symptomatic UTI patients in comparison to patients with asymptomatic bacteriuria (ASB) in SCI patients. Our hypothesis is that immune and neuronal mechanisms integrate to produce neuroimmune responses to ward off UTI, but not ASB. Therefore, changes in urinary NGF levels will reflect the status of the host immune response in lower urinary tract, whether related to ASB or UTI. NGF and its receptors may also amplify other immunoinflammatory and neuronal pathways contributing to bladder inflammation and symptoms associated with UTI.

1.5.2 Elevated Urine NGF Levels in Spinal Cord Injured Patients with Urinary Tract Infection (UTI) but not Asymptomatic Bacteriuria (iASB)

Table 2. Urinary NGF levels in 18 SCI patients.

Time	Urine samples	Urinary total NGF (pg/ml)	Urinary NGF/Cr	Statistics
Baseline ASB	18	4.6 \pm 1.5	0.1 \pm 0.1	
Week 1				
1. ASB and non UTI	13	8.3 \pm 2.1	0.2 \pm 0.1	$p=0.01^*$
2. Symptomatic UTI	5	77.8 \pm 17.3	1.1 \pm 0.5	$p=0.79^\#$
Week 2				
1. ASB and non UTI	9	5.1 \pm 1.8	0.1 \pm 0.1	$p<0.01^*$
2. Prev. symptomatic UTI treated with ABX and now asymptomatic	5	12.8 \pm 8.8	0.2 \pm 0.2	$p=0.04^{**}$
3. New onset Symptomatic UTI	4	85.6 \pm 42.2	1.3 \pm 1.0	$P= 0.75^{**}$

* comparison of urinary NGF/Cr level between the control and disease condition,

comparison of NGF/Cr level between baseline and time point, ** comparison between treated and post-treatment

A pilot study of 18 SCI men at an inpatient spinal cord injury center was carried out. The patients enrolled in the study were at their initial hospitalization after suffering from SCI due to: motor vehicle accidents 11, fall 4, diving 2, and work accident 1. Ten patients were paraplegic and 8 were quadriplegic with a mean age of 38.4 \pm 19 years old. All patients had indwelling catheters during their initial spinal shock phase and all patients demonstrated a positive urine culture (i.e. $>10^5$ colonies/cc). Twelve cultures grew out E. Coli, two cultures grew Staphylococcus aureus, three cultures grew Pseudomonas aeruginosa, and one culture was positive for Klebsiella. None of the men had a history of recurrent UTI's, incontinence, lower urinary tract symptoms, or renal dysfunction prior to SCI, except for one patient that had a renal calculus which passed spontaneously 4 years earlier and another patient that was a Type-2 diabetic.

Sample Purification: Urine was collected from the catheter by nurses from consented patients and an aliquot of urine specimens was sent immediately for urine culture. The remainder of the collected urine samples was immediately placed on ice to prevent degradation by endogenous proteases. Urine was centrifuged for 5 min at 10000 x g to remove cell particles and supernatants were passed through 0.34 mm Whatman chromatography paper. Filtrates were divided into aliquots and transported immediately to the -80°C freezer or maintained at 4°C until transported to the freezer within 4 hours. After removal of cell debris and nuclei, the supernatants underwent microscopic examination with a hemacytometry counting chamber to verify absence of cells or particles.

Using traditional ELISA technique, we investigated the levels of NGF in the urine of ASB and UTI patients. The samples were assayed in triplicate by antigen capture ELISA (Promega, Madison, WI) according to the manufacturer's instructions. The results as shown in Table 2 noted a significant five fold elevation of normalized NGF in UTI versus ASB patients. This was confirmed on two separate group of patients at one and two weeks post catheterization with development of UTI symptoms including new onset of urine leakage around catheter (n=4), new onset bladder spasm (n=4), fever (n=2), and increase in WBC count to above normal range (n=3). A greater than 5 fold elevation of NGF in the urine of UTI patients relative to ASB indicates that NGF is an important mediator of host response towards infection. Moreover, oral antibiotic treatment of five patients with symptomatic UTI for one week significantly decreased the elevated urine NGF relative to values obtained before antibiotic treatment. These results suggest that neuronal mechanisms are important in UTI and subsequent symptoms of urinary frequency. Urinary tract induced release of NGF is likely to lead to short and long term changes in the distribution and reactivity of sensory nerves across the lower urinary tract, promoting exaggerated inflammatory reactions during and after the infection.

On the basis of these observations, we postulate that changes of neurotrophin expression such as NGF in the lower urinary tract may represent an opportunity to separate ASB from UTI. In summary, a biomarker panel developed using a combination of NGF and selected chemokines can be a useful measure in differential diagnosis of UTI versus ASB. It can also be useful as a prognostic indicator of bacteriuria invasion of bladder wall with development of bladder inflammation response that may help judicious use of antibiotic therapy and curb the menace of bacterial resistance.

1.5.3 Urine Chemokine and Growth Factor Levels in Neurogenic Bladder Patients

In a different set of 13 patients with NGB collected from a different clinical site, with a history of SCI or other neurological diseases like MS or diabetes, we analyzed urinary chemokines and growth factors in addition to NGF in a single time point urine specimen, processed similar to NGF analysis above. We were able to consistently detect the following proteins in the urine of these patients: interleukin IL-5, IL-6, IL-1Ra, sIL-2R α , CC chemokines including MCP-1, MIP-1 β , RANTES(Regulated upon Activation, Normal T Expressed and Secreted), CXC chemokines including GRO- α / CXCL1, IL-8, and IP-10 and growth factors including vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet derived growth factor (PDGF-AA), VEGF, PDGF, and NGF (Figure 3). [Jacobs et al 2010]. The detected proteins were part of a screen composed of 32 proteins. Levels of urinary proteins were normalized to the concentration of creatinine (Cr). We will target these proteins to evaluate the effect that ONAbNT-A or oxybutynin ER has on their expression in urine. The selected proteins can be categorized as:

Afferent sensitizers: NGF, MCP-1, IP-10

Pro-inflammatory chemokines/ cytokines: IL-5, IL-6, GRO-a, IL-8, RANTES, MIP-1b,

Angiogenesis mediators: VEGF, PDGF

Ant-inflammatory Proteins: IL-1RA, sIL-2Ra

1.5.4 Changes in Urine Biomarker Levels with Treatment

To demonstrate our ability to detect treatment related changes in urinary proteins, we present data gathered from our pilot study in patients with another model of bladder dysfunction (i.e. interstitial cystitis/painful bladder syndrome (IC/PBS)) implanted with the InterStim® neuromodulator. In contrast to neuromodulation achieved by pharmacological method (ONAbNT-A), the neuromodulation of IC/PBS patients was achieved by physical means using electrical stimulation of afferent nerve fibers by calibrated frequencies of an implanted neurostimulator device (i.e. InterStim®). IC/PBS patients recruited for the study had symptoms of urinary urgency and frequency and bladder pain for at least 3 of the 6 months immediately before the first visit. Enrolled patients had O'Leary-Sant Interstitial Cystitis Symptom Index (i.e. ICSI) and Interstitial Cystitis Problem Index (i.e. ICPI) scores of 20 or higher and patients with pelvic mass, pelvic prolapse, urinary retention, and pelvic malignancies as revealed by physical examination were excluded. Clean catch midstream urine specimens was obtained from patients at baseline (prior to implant of interstim) and at 4, 12, and 24 weeks after implant. Enrolled patients also provided ICSI and ICPI scores at each time a urine specimen was collected. Urine samples were collected in 50ml conical tubes and then centrifuged for 10 minutes at 5,000 x g to remove cells as sediment. Supernatant was removed and divided into 1.5 ml aliquots (cryotubes) and transported immediately to the -80°C freezer or maintained at 4°C until transported to a -80°C freezer within 4 hours. The technique used to measure urinary proteins is illustrated in figure 4.

The decline in urinary chemokines of IC/PBS patients with InterStim treatment correlated with decreased ICSI scores suggesting that symptomatic improvements in a patient's condition measured by the subjective scale of ICSI score was associated with objective measures of temporal changes in urinary levels of chemokines and growth factors. It was clearly apparent that IC/PBS disease is heterogeneous in nature and the patients' respond differently to the same degree of neuromodulation. Variable patient response to electrical as well as to chemical neuromodulation (i.e. injection of botulinum neurotoxin) emphasizes the need for personalized objective monitoring of patients subjected to these treatments using biomarkers.

In summary, use of a multiplexed immunoassay panel (Luminex xMap system) demonstrates its utility in serving the stated objectives of this proposal. The antibody specificity of multiplex immunoassay offers simultaneous analysis of a set of markers that can form a fingerprint of a patient responding to treatment with improved sensitivity and specificity. Multiplexed immunoassays (Luminex) have allowed the measurement of biomarkers associated with bladder dysfunction with very low concentrations in urine that could not be measured for full patient cohorts with conventional immunoassays. These techniques also allow simultaneous evaluation of multiple biomarkers in microlitre volumes of urine sample.

2. STUDY DRUGS

2.1. ONAbNT-A (onabotulinumtoxin A, Botox®, Allergan Inc., Irvine, CA)

ONAbNT-A will be the active formulation. Each vial of ONAbNT-A Purified Neurotoxin Complex, Formulation No. 9060X, contains: 100 units (U) of *Clostridium botulinum* toxin type A,

0.5 mg albumin (human), and 0.9 mg sodium chloride in a sterile, vacuum-dried form without a preservative. One U corresponds to the calculated median lethal intraperitoneal dose (LD50) in mice. A 0.9% sterile saline (without preservative) for injection will be used as diluent for ONAboNT-A.

The ONAboNT-A treatment will be administered once as 20 injections each of 1 mL (10U/ml), evenly distributed into the bladder.

Side Effects: ONAboNT-A: It is expected that some participants may have some or all of the following side effects when given ONAboNT-A. Other side effects may occur which were not seen before. Side effects are usually temporary and manageable. However, it is possible they could cause serious disease or death. The study may include risks that are unknown at this time.

Based on the results of the experimental testing in animals, there may have an increased risk of development of bladder stones.

There have been rare reports of serious and/or immediate or even deadly abnormally sensitive reactions after treatment with ONAboNT-A. These reactions include allergic reaction, skin rash, itching, swelling, and difficulty in breathing.

It is a rare possibility that the injection of ONAboNT-A could lead to botulism. The classic symptoms of botulism include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. The doctor's examination may reveal that the gag reflex and the deep tendon reflexes like the knee jerk are decreased or absent.

There have been rare reports of sudden death, sometimes associated with difficulty in swallowing or pneumonia. There have also been rare reports of heart problems (including irregular heartbeats and heart attack, some resulting in death). Some of these patients were already at risk for heart disease. It is not known if ONAboNT-A actually caused these problems.

It should not be used when infection is present at the injection site or in people known to be abnormally sensitive to ONAboNT-A.

The following events have been observed since it has been marketed: skin rash, itching, and allergic reaction. In general, these side effects occur within the first week following injection and, while usually temporary, they may last several months. Pain, tenderness, or bruising around the injection site may also occur. Local weakness of the injected muscle(s) is expected. Weakness of nearby muscles may also occur due to spread of ONAboNT-A.

ONAboNT-A contains albumin, which comes from human blood. Although the blood is rigorously tested, there is an extremely remote risk for the transmission of viruses and similar infectious agents.

ONAboNT-A placebo (saline) will be the control formulation.

2.2. Oxybutynin Chloride ER (Ditropan XL[®], Teva Pharmaceuticals USA, Sellersville, PA)

Oxybutynin Chloride ER in a 10 mg capsule will be taken twice daily for the course of the study.

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (anti-nicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that Oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Common Side Effects: Blurred vision; constipation; diarrhea; dizziness; drowsiness; dry eyes, nose, skin, or mouth; headache; indigestion; nausea; runny nose; stomach pain or upset; trouble sleeping; weakness.

Severe Side Effects: Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); confusion; difficult or painful urination; fast or irregular heartbeat; fever; hallucinations; mental or mood changes (e.g., agitation); seizures; swelling of the hands, ankles, or feet; vision problems.

Oxybutynin chloride is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin chloride is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

The concomitant use of Oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

The safety of Oxybutynin chloride administered to women who are or who may become pregnant or are breastfeeding has not been established. Therefore, Oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Placebo oxybutynin will be compounded to match the oxybutynin.

The study drugs, ONAboNT-A, ONAboNT-A placebo, Oxybutynin, Oxybutynin placebo will be prepared for randomization by investigational pharmacy. The pharmacy will maintain the drug accountability, perform the randomization, and provide the study drugs to the PI. At the completion of the study, the pharmacy will dispose of unused drug per their standard operating procedures.

3. PURPOSE

This purpose of this clinical research study is to evaluate the safety and efficacy of 200 U ONAboNT-A injected into the detrusor versus oral oxybutynin for the treatment of urinary incontinence (UI) caused by neurogenic detrusor overactivity (NDO) in spinal cord injured volunteers. At baseline and each follow-up period, urine will be collected for analysis of biomarkers for nerve growth factor (NGF) and chemokines/cytokines to determine the potential role of urine biomarkers as patient selection and surrogate endpoints of treatment outcome predictors.

4. STUDY DESIGN

This will be a Phase 3B, double-blind, randomized, placebo-controlled, parallel-group study to assess the safety and efficacy of ONAboNT-A or 10 mg twice a day of oral oxybutynin hydrochloride ER in spinal cord injured volunteers diagnosed with neurogenic detrusor overactivity.

5. STUDY POPULATION

A total of 36 volunteers will be recruited for this study. Volunteers will include both males and females with spinal cord injuries who are 18 to 80 years of age and diagnosed with neurogenic detrusor overactivity. The volunteers will be patients at TIRR Memorial Hermann in Houston, TX. There are no eligibility restrictions as to race or ethnicity.

6. RANDOMIZATION

Volunteers will be randomized using a blocked randomization approach designed by the statistician and implemented by the investigational pharmacy: ARM 1: ONAboNT-A 200 U bladder injection and placebo oral capsule daily or ARM 2: Placebo bladder injection (saline) and oxybutynin ER 10mg capsule twice daily. Subjects will be randomized into one of the two treatment arms, using a block size of 4. The order in which the treatments are assigned in each block is randomized and this process is repeated for consecutive blocks of subjects until all subjects are randomized. This process ensures that after every fourth randomized subject, the number of subjects in each treatment group is equal.

7. ELIGIBILITY CRITERIA:

7.1. Inclusion

To be included in the study, volunteer must meet the following criteria at screening and Randomization/Day 1:

1. Volunteer is male or female, aged 18 to 80 years old.
2. Volunteer weighs at least 50 kg (110 lb) or more.
3. Written informed consent has been obtained.
4. Written Authorization for Use and Release of Health and Research Study Information has been obtained.
5. Volunteer has urinary incontinence as a result of neurogenic detrusor overactivity for a period of at least 3 months prior to screening as a result of spinal cord injury determined by documented patient history.

6. Spinal cord injury volunteers must have a stable neurological injury occurring at least 6 months or more prior to screening.
7. Volunteer has detrusor overactivity (defined as a phasic rise in bladder pressure during the filling phase determined by urodynamics) demonstrated during the screening period or within 1 year of screening.
8. Volunteer is able to complete study requirements including bladder diary completion and attend all study visits (telephone and clinic), in the opinion of the investigator.
9. Volunteer has a negative pregnancy result if female and of childbearing potential.

The following criteria are also required for entry into the study at Randomization/Day 1:

10. Volunteer experiences at least 14 episodes or more of urinary incontinence per week, including urinary incontinence between scheduled intermittent catheterization, with no more than 2 incontinent-free days, determined by completion of bladder diary during the screening period.
11. Volunteer currently uses or is willing to use clean intermittent catheterization (CIC) to empty the bladder (indwelling catheter is not permitted). Volunteers currently on CIC should be willing to maintain an established CIC frequency throughout the study. Caregiver may perform CIC.
12. Volunteers with a negative urine culture result must take an antibiotic medication for 3 days immediately prior to Randomization/Day 1, on Randomization/Day 1, and agree to continue antibiotic medication for at least 3 days following treatment. Volunteers with a positive urine culture result indicating urinary tract infection (UTI), must take an antibiotic to which the identified organism is sensitive for at least 3 days immediately prior to Randomization/Day 1, on Randomization/Day 1, and continue for 3 days following the procedure (or longer as needed). Antibiotics should be taken for at least 7 days. A UTI is defined as either a positive urine culture result with a bacteriuria count of more than 10^5 CFU/mL conjoint with a leukocyturia more than 5/hpf at screening with urinary tract symptoms or a positive urine culture that, in the investigator's opinion, requires antibiotic therapy.

7.2. Exclusion

Volunteers will be excluded from the study for any of the following criteria at screening or Randomization/Day 1:

1. Volunteer has history or evidence of any pelvic or urological abnormalities including but not limited to the following:
 - elevated serum creatinine more than 2 times the upper limit of normal (reference range)
 - current or history of hematuria, 1) if the hematuria is determined to be a pathologic condition or 2) is uninvestigated
 - interstitial cystitis in the opinion of the investigator
 - bladder stones within 6 months of screening
 - surgery or bladder disease other than detrusor overactivity that may impact bladder function with the exception of surgeries for bladder stones

- (more than 6 months) and stress incontinence, uterine prolapse, rectocele, or cystocele (more than 1 year) from screening.
2. Volunteer has had previous or current botulinum toxin therapy of any serotype for any urological condition within 9 months.
 3. Volunteer has a significant stress component to their urinary incontinence (i.e. stress urinary incontinence) in the opinion of the principal investigator.
 4. Volunteer has a history of narrow angle glaucoma that would preclude use of antimuscarinic medication.
 5. Volunteer has been immunized for any botulinum toxin serotype.
 6. Volunteer discontinued anticholinergic medication for overactive bladder less than 14 days prior to Randomization/Day 1.
 7. Volunteer has a history or current diagnosis of bladder cancer or has urine cytology results which may indicate bladder cancer not ruled out by investigator at Randomization/Day 1. Suspicious urine cytology abnormalities require the investigator's assessment to ensure that the findings are not indicative of malignancy.
 8. Volunteer is male with previous or current diagnosis of prostate cancer PSA level > 10.0 ng/mL. Volunteers with a PSA level equal to or greater than 4.0 ng/mL and equal to or less than 10.0 ng/mL must have prostate cancer ruled out to the satisfaction of the investigator according to local site practice. PSA age to be checked is on male patients 50 years or older, unless has a family history of prostate cancer or is of African American descent then PSA age to be checked is at age 40 years old.
 9. Volunteer has 24 hour total volume voided/catheterized more than 3000 mL of urine determined by completion of bladder diary collected over one consecutive 24 hour period during the 7 day diary collection period prior to Randomization/Day 1.
 10. Volunteer has an active genital infection, other than genital warts, either concurrently or within 4 weeks prior to screening.
 11. Volunteer uses any anti-platelet or anticoagulant therapy or is using medications with anticoagulative effects within 3 days prior to treatment. Some medications may need to be withheld for more than 3 days per clinical judgment of the investigator.
 12. Volunteer has hemophilia or other clotting factor deficiencies or disorders that cause bleeding diatheses.
 13. Volunteer has had concurrent treatment or treatment within 6 months of Randomization/Day 1 with capsaicin or resiniferatoxin.
 14. Volunteer is currently using or plans to use an implanted or non-implantable electrostimulation/neuromodulation device for treatment of overactive bladder.
 15. Volunteer has a known allergy or sensitivity to any components of the study medication, anesthetics or antibiotics or any other products associated with the treatment and general study procedures.
 16. Volunteer has any medical condition that may put the volunteer at increased risk with exposure to ONAboNT-A including diagnosed myasthenia gravis, Eaton-Lambert syndrome or amyotrophic lateral sclerosis.
 17. Volunteer is female and pregnant, nursing or planning a pregnancy during the study, or of childbearing potential and unable or unwilling to use a reliable form of contraception during the study.

18. Volunteer is currently or has previously participated in another therapeutic drug or device study within 30 days of screening.
19. Volunteer has any condition or situation which, in the investigator's opinion, puts the volunteer at significant risk, could confound the study results, or may interfere significantly with the volunteer's participation in the study.

8. RECRUITMENT PROCESS

The volunteers will be identified from the Spinal Cord Injury or the Urology Clinic at TIRR Memorial Hermann. They will be initially approached by their spinal cord injury or urology clinic physicians for recruitment into the study. If they wish to participate in this study, they will then be approached by Dr. Smith or his research staff. The study will be published on the BCM clinical trials websites. BCM's site is <http://www.bcm.edu/clinicalstudies/?PMID=7201>. The study will also be listed on ClinicalTrials.gov.

Advertising brochures will be placed in the Urology and SCI Clinics and included in a mail out planned for potential subjects. An advertisement will be placed on the Craig's List website.

9. INFORMED CONSENT PROCESS (See APPENDIX I)

Volunteers will be informed both verbally and in written form of the study and procedures involved and be given adequate opportunity to read it and discuss with family before it is signed. The PI and designated study staff will obtain a signed/dated Informed Consent Document (ICD) before enrolling each volunteer. The original signed/dated ICD will be kept with the research study documents, a copy will be given to the volunteer, and a copy will be placed in the volunteer's electronic medical record. The subjects consented at TIRR will have their ICDs scanned into a Master File located on a server that is managed and protected by the BCM IT department. The BCM's ICD provides a signature line for a volunteer's Legally Authorized Representative if applicable. Each patient executing an informed consent document will be given a unique consecutive number beginning with the number 001.

10. STUDY PROCEDURES (See APPENDIX II)

10.1 Screening - Visit 1

After informed consent is obtained, the following will occur at least 2 weeks but not more than 4 weeks prior to randomization/treatment:

- Inclusion/Exclusion criteria
- History and Physical Exam, including vital signs, weight
- Assessment of concurrent medications/procedures
- Kidney ultrasound or results of exam conducted within 1 year of enrollment
- Post void residual (PVR) in volunteers who micturate or have a mixed catheterization/micturition pattern
- Urine specimen to conduct urinalysis, urine culture and sensitivity
- CBC (Complete Blood Count)
- CMP (Complete Metabolic Panel)
- Pregnancy test - serum (for females only)

- Prostate specific antigen (for males only) PSA age to be checked is on male patients 50 years or older, unless has a family history of prostate cancer or is of African American decent then PSA age to be checked is at age 40 years old.
- OAB-Patient Satisfaction with Treatment Questionnaire (OAB_PSTQ)
- Urodynamic studies (if not performed 1 year prior to the Randomization Visit): This procedure measures bladder function. Lubricated catheters with pressure sensors are placed through the urethra into the bladder under sterile conditions and into the rectum.

The volunteer will then be placed in the sitting position and the pressure transducers will be leveled with the pubic symphysis.

The pressures bladder (Pves) and rectum (Pabd) are measured while the bladder is filled with saline at 40ml/min. The urodynamic machine will also record the subtracted detrusor pressure ($P_{det} = P_{ves} - P_{abd}$). Where the Pabd pressure is adjusted at baseline to render $P_{det} = 0$ by manipulation of the amount of fluid in the rectal balloon. The study will be performed following the guidelines of good urodynamics practices from the International continence society [Schafer et al, 2202; Paralyzed Veterans of America/Consortium for Spinal Cord Medicine, 2001].

The volunteer will be asked to perform several maneuvers during the procedure. These include:

- 1) Coughing (or bearing-down) several times during this procedure to make sure the equipment is working properly
- 2) Trying to suppress overactive bladder contractions, if present with sensation to stop voiding during the contractions.
- 3) To tell the urodynamicist when the bladder is maximally full.

The urodynamic study will take about 20-30 minutes to complete, with about 20 - 30 minutes of additional setup time.

Urodynamic parameters measured are baseline pressure, volume at first involuntary detrusor contraction, Peak detrusor pressure during first involuntary detrusor contraction, Maximum cystometric capacity, end fill pressure at maximum cystometric capacity or at the involuntary detrusor contraction used to determine maximum cystometric capacity and detrusor compliance.

- Volunteers will be instructed to complete a bladder diary for 7 consecutive days prior to next visit (Appendix IV)
- Dispense an antibiotic [Bactrim DS 1 tab twice a day] with instructions to take for 3 days prior to treatment (Day 1), on Day 1, and for 3 days following treatment day (total of 7 days). If subject has an allergy to sulfa or if urine culture indicates Bactrim resistant, another drug may be substituted.
- Volunteers will be instructed to stop taking medications for overactive bladder symptoms two weeks prior to injection.

10.2. Study Procedures/Study Interventions

10.2.1. Randomization and Treatment -Visit 2 (14 days to 6 weeks from Visit 1)

Volunteers will be reviewed for eligibility criteria. The following assessments will take place prior to randomization:

- Vital signs
- Urine Pregnancy test (for females only). If positive, a serum pregnancy test will be conducted to confirm.
- Urinalysis
- Post void residual in volunteers who micturate or have a mixed catheterization/micturition pattern
- Confirmation that overactive bladder medications were not taken 2 weeks prior to this visit.
- Assessment of concurrent procedures/medications, and adverse events
- Review of bladder diary
- Antibiotic drug accountability to assess compliance in taking of antibiotics

Volunteers will then be randomized to one of the two treatment groups. The following activities will take place prior to treatment:

- Urine collection for biomarker assessment
- Incontinence Quality of Life Instrument (I-QOL) and Incontinence Quality of Life Instrument (I-QOL) neurogenic module questionnaires will be completed. (See APPENDICES V-VIII: Questionnaires)

After randomization, the following events will occur:

- Bladder injection (with ONAboNT-A or saline) and initiation of oral therapy (with oxybutynin ER or placebo).
- All volunteers will be observed for at least 30 minutes after treatment prior to discharge.
- Volunteers will be instructed to continue oral antibiotics for 3 days.
- All volunteers will be instructed to complete a bladder diary for 7 consecutive days in the week prior to next visit.

10.2.1.1 Injection Procedures

10.2.1.1.a. Treatment Allocation, Use and Preparation

Volunteers will receive either ONAboNT-A 200 U or saline injection according to randomization to treatment sequence. Drug will be reconstituted/prepared by the investigational pharmacist at TIRR.

10.2.1.1.b. Administration

10.1.1.1.b.1. Study Treatment Anesthesia

The use of anesthesia during the injection procedure is determined by the investigator based on the medical need of the volunteer (e.g., tolerance to the procedure, spasticity, risk of autonomic dysreflexia, etc.). Preventative measures regarding autonomic dysreflexia are permitted per local site practice.

The following options are permitted:

- No anesthesia
- Local anesthesia: instillation of the bladder with 1-2% lidocaine (or similar acting agent) for at least 15 minutes in order to achieve sufficient anesthesia in patients with sensate bladders or at risk for autonomic dysreflexia.
- Prior to treatment administration, the bladder should be drained of lidocaine, rinsed with saline and drained again
- Sedation may also be administered according to local site practice if deemed medically necessary
- General anesthesia: general anesthesia may be used according to local site practice by an appropriately qualified anesthesiologist. However, the use of neuromuscular blocking agents is not permitted.

10.2.2. Treatment Procedure

- The investigator should confirm that the volunteer has taken their pretreatment antibiotics as specified.
- Laboratory results must be reviewed and evaluated by the investigator indicating that they were found to be acceptable prior to treatment, including a negative serum pregnancy test for women of childbearing potential. Volunteers should continue to meet inclusion and exclusion criteria.
- Questionnaires must be completed prior to treatment.
- A flexible or rigid cystoscope may be used for study treatment injections. The bladder should be instilled with a sufficient amount of saline in order to achieve adequate visualization for the study injections.
- The investigator will receive 2 identically appearing syringes pre-filled with approximately 10 mL each of reconstituted study medication (200 U of ONAboNT-A in 20ml of preservative free saline or 20 ml preservative free saline) from the independent reconstitutor. The first syringe should be attached to the injection needle. The injection needle can then be inserted into the injection port of the cystoscope for detrusor injections. Under direct visualization, injections should be distributed evenly across the detrusor walls spaced approximately 1 cm apart to include the trigone. The needle should be inserted approximately 2 mm into the detrusor for injections. The entire 20 mL will be administered as 20 injections each of 1 mL (total volume administered is 20 mL), evenly distributed into the detrusor via cystoscopy. The injection process will take approximately 15 minutes to complete. After the treatment is finished, the patient will remain in the clinic for at least 30 minutes for observation. Also, he/she will be asked to urinate before leaving the office. If the patient cannot satisfactorily urinate to empty his/her bladder [i.e. urinary retention], a temporary catheter may be used to drain the bladder. (See APPENDIX IX: Injection Pattern Diagram)
- All volunteers must be observed for at least 30 minutes following the study treatment administration. Safety monitoring and assessments are to be done according to local site practice (e.g., monitoring of blood pressure, pulse rate and ensuring that volunteer has emptied the bladder before leaving the site).
- Spinal cord injury volunteers with lesions above the T6 level are particularly at risk of developing autonomic dysreflexia, which presents with symptoms of increased blood pressure, relative bradycardia, headache, and skin flushing [Blackmer, 2003]. Should autonomic dysreflexia develop in a volunteer, the condition should be immediately handled according to local site practice. An occurrence of autonomic dysreflexia during study drug administration will be reported as an adverse event. Guidelines for managing autonomic

dysreflexia will be included in the Investigator Binder [Paralyzed Veterans of America/Consortium for Spinal Cord Medicine, 2001].

- Volunteers should be instructed to contact the study site if they experience any adverse events post-treatment.

10.3 Post Randomization/Treatment Visits (Follow Up) -Day 3, and Weeks 4, 12, and 24 (\pm 3 days) post randomization/treatment

10.3.1 Visit 3: Day 3 to 5 post randomization/treatment (Telephone Visit)

Discuss subject's well-being, concomitant medications, antibiotic compliance, and side-effects or adverse events.

10.3.2 Visits 4: Week 4 (\pm 3 days) post randomization/treatment

- Vital Signs
- PVR for volunteers who micturate or have a mixed catheterization/micturition pattern
- Urine collection for biomarker assessment
- Urinalysis, culture and sensitivity
- Collect bladder diary for Total Volume Voided assessment
- Collect oral study drug pill bottle.
- Urine pregnancy test (females). If positive, a serum pregnancy test will be conducted to confirm.
- Concurrent medications and procedures
- Adverse events assessment
- The I-QOL), (I-QOL) neurogenic module, OAB-Patient Satisfaction with Treatment Questionnaire (OAB_PSTQ), and Patient Global Assessment (PGA) questionnaires will be completed.
- Volunteer will be instructed to complete a bladder diary for 7 consecutive days in the week prior to next visit.
- Dispense oral study medicine with instructions to bring all unused medicine to next visit.

10.3.3. Visit 5: Week 12 (\pm 3 days) post randomization/treatment

- Same events and procedures as previous study visits plus urodynamic studies.

10.3.4. Visit 6: Week 24 (\pm 3 days) post randomization/treatment - End of Study Visit

- Physical Exam, including vital signs
- CMP (Complete Metabolic Panel)
- PVR for volunteers who micturate or have a mixed catheterization/micturition pattern
- Urine collection for urinalysis, culture and sensitivity, and biomarker assessment
- Study drug accountability
- Collect bladder diary
- Serum pregnancy test (females)
- Concurrent medications and procedures
- Adverse events assessment

– Questionnaires = I-QOL, I-QOL-Neurogenic Module, OAB-PSTQ, PGA

11. SAMPLE SIZE JUSTIFICATION

Data from a preliminary study in SCI patients showed that Ditropan XL (i.e. oxybutynin ER equivalent) reduced weekly urinary incontinence episodes at 12 weeks by 54% (i.e. from 13 to 6 per week). [Bennett et al., 2004] A second large randomized trial found that oxybutynin lowered incontinence episodes from 3.3 to 2 (i.e. 39%) after 21 days of treatment. [Stohrer et al, 2007] The most recent and largest efficacy and safety study demonstrated that ONAboNT-A reduced weekly urinary incontinence episodes by 69% at 6 weeks (i.e. from 30.5 to 9.5 per week). [Ginsberg et al, 2011] Our patient population will consist of patients having a relatively high number of weekly urinary incontinent episodes, similar to those in the Ginsberg study. Although our study groups will include a placebo pill and sham injection group we don't expect to see a significant placebo effect in our neurogenic bladder population as has been previously demonstrated in idiopathic (i.e. non-neurogenic) overactive bladder populations. For this study, we will assume a reduction of 69% in incontinence episodes for the ONAboNT-A group and a 45% reduction in the oxybutynin group (i.e. a value midway between the results of Bennett et al, 2004 and Stöhrer et al, 2007).

Our sample size assumptions include a mean baseline level of 30 weekly incontinent episodes, a 69% reduction of incontinent episodes in the ONAboNT-A + placebo pill group (i.e. post-treatment 9 incontinent episodes), a 45% reduction in the oxybutynin + sham injection group (i.e. post-treatment 17 incontinent episodes) at 12 weeks, an alpha level of 0.05, 80% power and a standard deviation of 50% of the mean. The resulting sample size of 18 subjects per group (total=36) is adjusted for an expected attrition of 20%. This effect was selected as the smallest effect that would be important to detect, in the sense that any smaller effect would not be of clinical or substantive significance. It is also assumed that this effect size is reasonable, in the sense that an effect of this magnitude could be anticipated based on previous findings.

12. DATA ANALYSIS

Initially, graphical methods will be used to assess distributional properties of the data (weekly urge incontinent episodes, urine biomarker levels, quality of life scores) and to examine patterns of correlations between observations at different time points. Measures such as age, gender, number of weekly urinary incontinence episodes, urine biomarker levels, I-QOL and I-QOL neurogenic questionnaires and disease severity will be examined using summary statistics to determine if any baseline differences exist between the 2 study groups. If extreme departures from normality are found, non-parametric methods such as the Wilcoxon rank-sum test or transformation of the data will be considered. Questionnaire scores will be examined for reliability using Cronbach's alpha. The distributions of the scores will be examined to see if they are evenly distributed around the mid-point of the scales or are clustered at the top or bottom of the scales (ceiling or floor effect). If strong ceiling or floor effects are found, this could limit the usefulness of these measures.

The primary endpoint is the reduction in mean weekly incontinent episodes in the ONAboNT-A treated group compared to the oxybutynin treated group at 12 weeks. The change between the 2 groups at 12 weeks will be analyzed using a general linear model approach with weekly urinary incontinent episodes as the outcome variable, treatment group as the independent variable with adjustment for baseline weekly urinary incontinent episodes, a baseline covariate. This approach is equivalent to the independent t-test, but allows adjustment for the baseline outcome levels. Exploratory growth curve analysis will be done to investigate the pattern

(linear, quadratic or possibly cubic) of change in incontinence episodes over time during the entire data collection period. Growth curve models have an assumption for multivariate normality of the dependent variables. If the data are not normally distributed but approximately follow some exponential distribution, then a generalized linear model using a generalized estimating equation can be applied. The generalized estimating equation links functions to allow maximum likelihood estimation for variables that follow a distribution from the exponential family other than the normal. [McCullagh and Nelder, 1989] The same hypotheses can be tested with these methods as with the normal growth curve model.

Secondary endpoints, such as quality of life scales, will be tabulated using cross tabulations and summary statistics. Measures of association such as chi-square and correlations will be used to assess differences in relationships between the control and intervention groups. Changes in these secondary measures between control and intervention groups at 12 weeks will be compared using independent t-tests or the Wilcoxon rank-sum test. Additionally, we will look at the longitudinal pattern of the questionnaires at baseline, 4, and 12 weeks using growth curve modeling to explore the trajectory of change. Statistical analysis will be done using SAS, version 9.2 software.

13. ENDPOINTS

The **Primary Endpoint** is the mean reduction in weekly incontinence episodes 12 weeks following treatment. **Secondary Endpoints** include improvements in quality of life scales (Incontinence Quality of Life Instrument (I-QOL), Incontinence Quality of Life Instrument Neurogenic Module, OAB-Patient Satisfaction with Treatment Questionnaire (OAB_PSTQ), and Patient Global Assessment (PGA), changes in maximum capacity by urodynamic study, as well as reductions in urine NGF and chemokine/cytokine levels (pg/ml normalized to creatinine). We will also correlate NGF and chemokine/cytokine levels with disease severity and treatment outcome. Other endpoints include detrusor compliance (DC) (ml/cm H₂O) by urodynamics, total volume voided recorded over one 24 hour period as recorded on bladder diary for all voids (catheterization and voluntary), and number of episodes per day of voiding and method (catheterization and voluntary) as recorded by bladder diary, and the frequency of asymptomatic bacteriuria (i.e. ASB) versus symptomatic UTI's. We will correlate NGF and chemokine/cytokine levels with disease severity, the presence of ASB versus symptomatic UTI, and treatment outcome.

14. LABORATORY EVALUATIONS

14.1. Specimens

Urinary levels of NGF, cytokines and chemokines will be measured at study visits 2, 4, 5, and 6. Urine will be collected by sterile catheter or clean catch midstream (CCMS) voided specimen. Specimens will be processed at the time of collection, de-identified with an untraceable number, and shipped to the Urology Research laboratory at William Beaumont Hospital, Royal Oak, MI, under the direction of Michael B. Chancellor, MD. The identification number will be used in research documents.

14.2 Specimen Preparation, Evaluation, and Analysis

The Urology Laboratory Manual (Appendix II) will provide specific information.

14.3. Confidentiality

The data will be stored with Dr. Chancellor in a locked office. Urine will only be identified by volunteer identification number and initials prior to shipping. Dr. Chancellor will not have access to any other patient identifiers. The urine will be placed into a minus 80 freezer in the locked urology research laboratory with restricted access to the Research Institute.

To ensure rigorous HIPPA compliance throughout the study, each urine specimen from the volunteers enrolled in the study will be stored in the urology biobank, which will de-identify the specimens with an untraceable number upon receiving the specimen to delink the volunteer clinical data from analysis team. This number will be used in research documents. All data will be stored in Dr. Chancellor locked office. The key to urine biobank number and volunteer identification number is held in Urology research office accessible only to Dr. Chancellor.

The risks from breach of confidentiality will be minimized by using de-identified volunteer specimens and the secured computer database maintained in the urology biobank will protect the identity of volunteers from the analytic team.

After research testing required for this study is completed, the remaining portion of urine samples will be stripped of the code and will be banked for future use. It will be kept until it is all gone. Samples will not be sold or transferred to anyone else. If at any time the subject withdraws from this study he will not be able to get his urine samples back because there is no identifying information on the samples.

15. DATA COLLECTION AND MANAGEMENT

15.1. Methods for Data Collection

Protocol-specific data will be collected on Case Report Forms and forwarded to the biostatistician for compilation by the data manager. The completed dataset is available to the investigators and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from BCM. (See APPENDIX XI: Case Report Forms)

15.2. Volunteer Identifiers

An unambiguous volunteer identification code will be used in lieu of the volunteer's name on all study data compiled. This volunteer identification code will include the volunteers' initials and volunteer number. A key for this code will be maintained by the Principal Investigator and kept separate from study files. All source documents and study data will be kept confidential. Study data will be kept in a locked file cabinet and/or password protected and encrypted computers and stored on servers managed by BCM IT.

15.3. Confidentiality

15.3.1 Baylor College of Medicine (BCM) and TIRR Memorial Hermann

The PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

Research data will be maintained by Dr. Smith in his office in the Baylor Urology Clinic.

Regulatory documents will be managed by Research Administration of the Scott Department of Urology, BCM located in 502/506D in the Jewish Wing of Main Baylor. The Faculty Center suite utilizes an electronic locking system for security purposes. The Main Baylor offices have keyed entries. All computers utilized for this study are password protected and encrypted. Data is stored on encrypted BCM servers that are managed by IT.

The BCM Scott Department of Urology complies fully with the HIPAA Privacy Rule.

Regulatory authorities that provide oversight of this clinical trial include IRBs, OHRP, and any other applicable state and local authorities will have access to the study data.

15.3.2. William Beaumont Hospital

All specimens will be shipped to the laboratory with only volunteers' initials and volunteer ID# as identifications. Dr. Chancellor will not have access to the key code list of volunteers.

15.4. Disposition of Data

To enable evaluations and/or audits from Health Authorities/BCM, the investigators agree to keep records, including the identity of all participating volunteers (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all CRF's, and detailed records of drug disposition. The requirements of the IRB will also be met.

15.5. Sharing Study Results

Volunteers may never be able to obtain limited research health information.

16. RISK/BENEFITS ASSESSMENT

16.1. Foreseeable Risks:

16.1.1. ONAboNT-A

It is expected that some participants may have some or all of the following side effects when given ONAboNT-A. Other side effects may occur which were not seen before. Side effects are usually temporary and manageable. However, it is possible they could cause serious disease or death. The study may include risks that are unknown at this time.

Based on the results of the experimental testing in animals, there may have an increased risk of development of bladder stones.

There have been rare reports of serious and/or immediate or even deadly abnormally sensitive reactions after treatment with ONAboNT-A. These reactions include allergic reaction, skin rash, itching, swelling, and difficulty in breathing.

It is a rare possibility that the injection of ONAboNT-A could lead to botulism. The classic symptoms of botulism include double vision, blurred vision, drooping eyelids, slurred speech,

difficulty swallowing, dry mouth, and muscle weakness. The doctor's examination may reveal that the gag reflex and the deep tendon reflexes like the knee jerk are decreased or absent.

There have been rare reports of sudden death, sometimes associated with difficulty in swallowing or pneumonia. There have also been rare reports of heart problems (including irregular heartbeats and heart attack, some resulting in death). Some of these patients were already at risk for heart disease. It is not known if ONAboNT-A actually caused these problems.

It should not be used when infection is present at the injection site or in people known to be abnormally sensitive to ONAboNT-A.

The following events have been observed since it has been marketed: skin rash, itching, and allergic reaction. In general, these side effects occur within the first week following injection and, while usually temporary, they may last several months. Pain, tenderness, or bruising around the injection site may also occur. Local weakness of the injected muscle(s) is expected. Weakness of nearby muscles may also occur due to spread of ONAboNT-A.

BOTOX contains albumin, which comes from human blood. Although the blood is rigorously tested, there is an extremely remote risk for the transmission of viruses and similar infectious agents.

16.1.2. Oxybutynin ER: Also known as Ditropan XL

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that Oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Common Side Effects: Blurred vision; constipation; diarrhea; dizziness; drowsiness; dry eyes, nose, skin, or mouth; headache; indigestion; nausea; runny nose; stomach pain or upset; trouble sleeping; weakness

Severe Side Effects: Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); confusion; difficult or painful urination; fast or irregular heartbeat; fever; hallucinations; mental or mood changes (e.g., agitation); seizures; swelling of the hands, ankles, or feet; vision problems.

Oxybutynin chloride is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin chloride is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

The concomitant use of Oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

The safety of Oxybutynin chloride administered to women who are or who may become pregnant or are breastfeeding has not been established. Therefore, Oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

16.1.3. Placebo

Since placebo has no active drug, the medical condition may become worse, stay the same or improve.

16.1.4. Antibiotics (CIPRO, or generic, 500 mg twice a day)

The most frequent side effects of ciprofloxacin include nausea, vomiting, diarrhea, abdominal pain, rash, headache, and restlessness. Rare allergic reactions have been described, such as hives and anaphylaxis (shock).

16.1.5. Cystoscopy with Bladder Injection

The discomfort is nearly identical to being catheterized, which generally causes slight to moderate discomfort. There will be a feeling of fullness in the bladder and a sensation to empty during the cystoscopy examination. Bleeding, infection, damage to urethra or surrounding structures may occur.

16.1.6. PVR

The risks of having a catheter placed in the bladder for draining the residual urine are infection of the urinary tract, injury to the urethra caused by rough insertion of the catheter, narrowing of the urethra due to scar tissue caused by the insertion of a catheter, injury to the bladder caused by incorrect insertion of the catheter.

16.1.7. Urodynamics

Generally the risks of a urodynamic study are low and are no more than those of a Foley Catheter insertion, which include the possibility of infection, trauma to the urethra or prostate, traumatic bleeding from the catheterization, discovery of previously unsuspected urethral stricture with inability to get the urodynamics catheter into the bladder.

Patients with a spinal cord injury generally occurring at the Thoracic 5 (T-5) level and above have a risk of experiencing autonomic dysreflexia during bladder filling during the urodynamic or study treatment procedures. To minimize this risk continuous blood pressure monitoring is performed throughout the study.

Autonomic dysreflexia can develop suddenly, and is a possible emergency situation. Symptoms of autonomic dysreflexia include the following: elevation in blood pressure, headache, goose pimples, sweating above the level of injury, nasal congestion, slow pulse, blotching of the skin, and restlessness. If not treated promptly and correctly, it may lead to seizures, stroke, and in some cases, even death.

16.1.8. Ultrasound

Ultrasound testing is painless and harmless but the volunteer might experience anxiety in anticipation of the test. Ultrasound tests involve no radiation and studies have not revealed any adverse effects.

16.1.9. Blood draw

Inserting needles into veins for collecting blood may be uncomfortable. Risks include slight bruising at the puncture site, fainting, the formation of a small blood clot or swelling of the vein and surrounding tissue, bleeding from the site, and the remote possibility of infection at the site of the needle puncture. Fainting is usually harmless, of short duration, and typically produces feelings of weakness, sweating, slowing of the heart rate and an abnormal decrease in blood pressure. Care will be taken to avoid these complications.

16.1.10. Questionnaires

Completing the questionnaires may cause you to have or to experience some level of emotional discomfort due to the personal nature of the questions. The study doctor and staff will maintain a professional and caring attitude while administering the questionnaires.

16.1.11. Confidentiality

The loss of confidentiality regarding research information is a possibility, although, the risk is extremely small. The investigator and his staff will make every effort to maintain the confidentiality.

16.1.12. Pregnancy

It is possible that the medicines used in this study could injure a fetus if volunteer or volunteer's partner becomes pregnant while taking them. Pregnant and/or lactating women will be excluded from the study. As outlined in the protocol, women of childbearing potential will be carefully screened with serum pregnancy testing within 48-72 hours prior to randomization and each treatment (s). Because of the potential risks involved, pregnancy should not occur during participation in this study. The following methods of contraception, if properly used, are generally considered reliable for females of childbearing potential who may participate in the study: oral contraceptives, patch contraceptives, injection contraceptives, male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation), vasectomized partner(s), or total sexual abstinence.

16.2. Risk Management and Emergency Response

16.2.1. Safety Measures

The following safety measures are included in the protocol in an effort to eliminate risks to volunteers:

- Physical examination
- Vital signs
- Urinalysis
- Urine culture and sensitivity
- Kidney ultrasound
- Post void residual (PVR) by bladder scan, ultrasound, or catheterization for volunteers who micturate or have a mixed catheterization/micturition pattern
- Serum pregnancy test for female volunteers of childbearing potential at screening, qualification for re-treatment if urine pregnancy is positive, and study exit
- Urine pregnancy test for female volunteers of childbearing potential on day of treatment (prior to each treatment). If positive, a serum pregnancy test will be conducted to confirm.
- Concurrent medications
- Concurrent procedures
- Serious medical events
- Adverse events

16.2.2. Health outcome measures

- Incontinence Quality of Life Instrument (I-QOL) [Patrick et al, 1999]: The I-QOL is a disease-specific, quality of life (QOL) questionnaire designed to measure QOL impact of urinary incontinence on volunteers. Designed for self-completion, the I-QOL takes approximately 5 minutes to complete. The I-QOL is scored as a total score, and 3 domain scores of Avoidance Limiting Behavior, Psychosocial Impact, and Social Embarrassment.
- Incontinence Quality of Life Instrument Neurogenic Module [Lee et al, 2005]: The I-QOL Neurogenic Module is designed to measure the impact of urinary incontinence on volunteer's lives in a neurogenic population.
- OAB Patient Satisfaction with Treatment Questionnaire (OAB-PSTQ): The OAB-PSTQ is a volunteer satisfaction with treatment questionnaire created by Allergan, Inc. Volunteers' goals and expectations from treatment are assessed.
- Patient Global Assessment (PGA): The PGA is a global volunteer assessment that assesses the volunteer's symptoms, quality of life, activity limitations and overall emotions.

16.2.3. Stopping Criteria

If moderate to severe adverse events occur after an injection of ONAboNT-A, then no further injection will be given. If moderate to severe adverse events occur due to the Oxybutynin, the medication will be stopped. Volunteers will be symptomatically treated and closely monitored after any moderate to severe adverse events.

In the event of an emergency, the research pharmacy will provide the unblinded information for the volunteer. Care will be provided to the volunteer at the VA Medical facility.

16.3. Potential benefits

Approximately 25 million Americans suffer from varying degrees of urinary incontinence with many of these being caused by neurogenic detrusor overactivity (NDO) in spinal cord injured patients. Antimuscarinic drugs, while effective in many patients, have significant adverse events

like dry mouth, constipation, and blurred vision that limit their utility. The potential benefits to the volunteer include improvement in the urinary incontinence symptoms, reduction in the rate of urinary tract infections, decrease in the number of required catheterizations, and an ease of the financial burden of buying protective garments.

The potential benefits to society in addition to those mentioned above would include the decrease in medical costs.

16.4. Intent to benefit

For volunteers that cannot give their own consent to participate in this study, an intent to benefit will be promulgated by the fact that each participant will be given the opportunity to receive ONAboNT-A injection after completing the study as standard of care for refractory NDO. We expect that ONAboNT-A will reduce urinary incontinence as well as its associated complications within our patient cohort.

16.5. Study-Related Injury

If any side effect or injury should occur, the participant should notify Dr. Smith at 713-798-4001 so that he can provide directs on how to receive appropriate medical treatment.

Research personnel will try to reduce, control, and treat any complications from this research. If a participant is injured because of this study, the participant or third party insurer is responsible for the medical care that is provided just like any other medical care.

17. WITHDRAWAL FROM THE PROTOCOL

Volunteers may discontinue participation in the study at any time without penalty or loss of benefits to which the volunteer is otherwise entitled. If possible, a volunteer who is withdrawing should complete the End of Study visit events/procedures. Volunteers participating in this study will receive \$50 for completing each of the study visits 2, 4, 5, and 6.

18. MODIFICATIONS TO THE PROTOCOL

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by BCM. Each amendment must be approved by all the principal investigators and each IRB, and if applicable, the local regulatory authority. Local requirements must be followed. If a protocol amendment requires a change to the Written Informed Consent Form, approval of the revised Written Informed Consent Form by the IRB is required before the revised form is used. The principal investigator is responsible for the distribution of these documents to his study staff and to appropriate institutional review committees.

Examples of amendments requiring such approval are:

- increases in drug dose or duration of exposure of volunteers,
- significant changes in the study design (e.g. addition or deletion of a control group),
- increases in the number of invasive procedures,
- addition or deletion of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all volunteers included in the

trial. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

Changes in the staff used to monitor trials
Minor changes in the packaging or labeling of study drug
Revisions to study forms

Any deviation to the protocol that may have an effect on the safety or rights of the volunteer or the integrity of the study must be promptly reported to the IRB and other required authorities. A deviation log will be maintained by the site. The log will be tabulated into a master log and submitted with each annual IRB renewal report.

19. REPORTING UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS/ OTHERS

Reporting of unanticipated problems will be in accordance to the current IRB guidelines and FDA regulations.

An adverse event log will be maintained at the clinical site. The logs will be tabulated into a master log and submitted with each annual IRB renewal report.

20. CONTINUING REVIEW AND FINAL REPORT

Annual IRB review submissions will be made according to the local IRB's guidelines and a final report will be submitted at the completion of the study. All approvals and/or communications between the IRB and site will be forwarded to the HRPO, and any additional authorities providing oversight of this study.

21. SURVEYS, QUESTIONNAIRES, AND OTHER DATA COLLECTION INSTRUMENTS

21.1. Informed Consent Document (ICD)

Each potential volunteer will review the informed consent document with the study personnel. If the potential volunteer is willing to participate and comply with the study's requirements, the ICD will be executed.

21.2. Voiding Diary

Volunteers will complete the Voiding Diary for 7 consecutive days in the week prior to their clinic visits.

21.3. Questionnaires

Volunteers will be requested to complete the following questionnaires:

21.3.1. Incontinence Quality of Life Instrument (I-QOL) [Patrick et al, 1999]:

The I-QOL is a disease-specific, quality of life (QOL) questionnaire designed to measure QOL impact of urinary incontinence on volunteers. Designed for self-completion, the I-QOL takes

approximately 5 minutes to complete. The I-QOL is scored as a total score, and 3 domain scores of Avoidance Limiting Behavior, Psychosocial Impact, and Social Embarrassment.

21.3.2. Incontinence Quality of Life Instrument Neurogenic Module [Lee et al, 2005]

The I-QOL Neurogenic Module is designed to measure the impact of urinary incontinence on volunteer's lives in a neurogenic population.

21.3.3. OAB Patient Satisfaction with Treatment Questionnaire (OAB-PSTQ)

The OAB-PSTQ is a volunteer satisfaction with treatment questionnaire created by Allergan, Inc. Volunteers' goals and expectations from treatment are assessed.

21.3.4. Patient Global Assessment (PGA)

The PGA is a global volunteer assessment that assesses the volunteer's symptoms, quality of life, activity limitations and overall emotions.

21.4. Case Report Forms (CRFs)

Protocol-specific data will be collected on Case Report Forms as required. The completed dataset is available to all the investigators, is the sole property of BCM, and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from BCM.

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APPENDIX I

SCHEDULE OF EVENTS

Schedule of Events

Events/Procedures	Consent/ Screening	Treatment and F-U Sequence				
	Visit 1 2 to 4 weeks prior to Visit 2	Visit 2 Randomization and Injection Day 1 V 1 +14 Days to 6 Weeks	Visit 3 Telephone 3-5 Days Post-Injection	Visit 4 4 wks Post-injection ± 3 days	Visit 5 12 wks Post-injection ± 3 days	Visit 6 End of Study 24 wks Post-injection ± 3 days
Consent	X					
Inclusion/exclusion	X	X				
Concomitant medications	X	X	X	X	X	X
Physical exam	X					X
Vital signs	X	X		X	X	X
Weight	X					
CBC	X					
CMP	X					X
PSA (Males Only)	X**					
Serum Pregnancy test (Females)	X	X*		X*	X*	X
Urine Pregnancy test (Females)		X		X	X	
Post void residual	X	X		X	X	X
Kidney ultrasound within 1 year	X					X
Urodynamic studies within 1 year	X				X	
Urinalysis	X	X		X	X	X
Urine C&S	X			X	X	X
Urine specimen collection for biomarker evaluation		X		X	X	X
Off meds for 2 weeks prior to injection		X				
Bladder diary	X	X		X	X	X
Assessment of total volume voided on diary		X		X	X	X
OnaBoNT-A/Placebo Injection		X				
Dispense Oxybutynin/Placebo		X		X	X	
Study product Accountability				X	X	X
Antibiotic prescription	X					
Antibiotic Accountability		X				
I-QOL		X		X	X	X
I-QOL neurogenic module		X		X	X	X
OAB-PSTQ	X			X	X	X
Patient Global Assessment				X	X	X
Adverse event assessments		X	X	X	X	X
Subject stipend for transportation		X		X	X	X

*Serum Pregnancy will be done if urine pregnancy is result is positive

PSA- **50 years or older, unless has a family history of prostate cancer or is of African American decent then PSA age to be checked is at age 40 years old

Non-standard of care is highlighted in yellow.

APPENDIX II

URINE COLLECTION PROTOCOL

**ONAbNT-A v. Oral Oxybutynin in Spinal
Cord Injured Patients with NDO
(#11-09-10-04)**

URINE COLLECTION PROTOCOL

URINE COLLECTION AND PROCESSING PROTOCOL

Samples should be processed immediately and submitted to William Beaumont Health System when a set of urine specimens from a batch of 10 patients or a reasonable size batch is complete:

1. Record the date, time of collection and the time you start sample processing on sample form.
2. Divide urine equally between two 50ml tubes of undiluted urine collected preferably from volunteers when they feel a full sensation or the need to catheterize will be used for analysis.
3. For the urine sample to be preserved (one of the 50 ml tubes):
4. Carefully cut the tip off the Norgen Urine Preservative Single Dose ampule and dispense the contents into one of the 50mL conical tubes with the urine sample. Tighten container lid. Invert several times to mix.
5. From the tube with urine+preservative, aliquot 5 mL into a pre-labeled tube.
6. Make sure both containers are securely closed and will not leak by carefully inverting. Tubes should have "P" on the label.
7. Wrap with parafilm the lids of both the 50mL tube and 5mL tube with preserved urine (this is done in case there is a leak).
8. Place in biohazard bag with absorbent material.
9. Store at room temperature out of direct light.
10. For the urine sample to be frozen (the other 50mL tube):
 - a. Spin the sample 10 min @ 650 x g at 4°C.
 - b. During the spin, add 10uL of BME to 1mL of Buffer SK and ensure all tubes to be used are labeled.
 - c. Pour off the supernatant carefully into a new 50mL tube as not to disturb or dislodge the cell pellet.
 - d. To cell pellet: Add 350 µL of Buffer SK with BME to the pellet. Lyse cells by vortexing for 15 seconds. Ensure that the entire pellet is completely dissolved before proceeding to the next step. Transfer the lysate to an RNase-free microcentrifuge tube. Add 200 µL of 100% ethanol to the lysate. Mix by vortexing for 10 seconds. Store at -80°C. Tube should have "RNA" on label.
 - e. To urine supernatant: Aliquot 1mL into ten (10) 1.5mL microcentrifuge tubes. Store at -80°C.
 - f. Discard any remaining urine.
4. Collection should immediately be placed on ice to halt enzymatic activity. Store on ice until processing. Process within 30 to 60 minutes or as soon as possible.
5. Ship OVERNIGHT with AM delivery in sufficient **DRY ICE** to:

Dr. Laura Lamb
William Beaumont Hospital Research Institute
3811 West 13 Mile Road
Royal Oak, MI 48073
(248) 551-6226

Contact several days before shipping:

Dr. Laura Lamb	laura.lamb@beaumont.org	248-551-0579
Sarah Bartolone	sarah.bartolone@beaumont.org	248-551-6226

Labeling of Tubes

- All tubes should have study ID number and date collected on them.
- For samples containing urine + preservative, after sample ID number put “-P” (e.g. 103-P). There will be one 50mL tube and one 5mL tube total.
- For sample containing urine + Buffer SK + BME + Ethanol, after sample ID put “RNA” (e.g. 103 RNA). There will be one 1.5mL tube total.
- For sample containing urine supernatant, no additional labeling is needed (e.g. 103). There will be ten 1.5mL tubes total.

URINE SAMPLE ACQUISITION FORM

(to be filled and submitted with each sample)

H #: 34972

Subject ID#: _____

Date of collection: _____

Time of collection: _____

Time samples were frozen: _____

Time started sample processing: _____

- Preservative added to 50ml sample: Yes No
- 5ml aliquot of preserved urine aliquoted: Yes No
- BME added to Buffer SK: Yes No
- Buffer SK +BME and Ethanol added to pellet: Yes No
- 10 aliquots of frozen urine made: Yes No
- Preserved samples stored at room temperature: Yes No
- Frozen Samples stored at -80 degrees C: Yes No

Time sample completed: _____

Any Additional Notes:

Name (Printed)

Signature

Date

APPENDIX III

VOIDING DIARY

**BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders
7-DAY DIARY**

Volunteer ID# _____ Visit # _____

The diary is to be completed for the 7 days in a row the week before your clinic visit. Write the current date and diary day in the **DATE** row for each day.

At the time you experience an accidental leakage of urine, rate the episode as follows in the **Leakage** column:

1 = damp or a few drops of urine

2 = wet your underwear or pad

3 = soaked underwear/clothes or emptied bladder. You may have several accidents during an hour. Please record each event.

In the **Void** column, place a check mark (√) each time you urinate in the toilet.

In the **CIC** column, please place a check each time you catheterize.

In the **Amount** column, indicate each time the number of ccs you urinated **OR** catheterized

DATE	TIME	Leakage	Void	CIC	Amount
10/1/10	12am-3:59am			√	175
	4am-4:59am				
	5am-5:59am				
	6am-6:59am			√	300
	7am-7:59am				
	8am-8:59am	1, 2			
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm	3, 1, 1			
	1pm-1:59pm				
	2pm-2:59pm			√	100
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm			√	200
	7pm-7:59pm				
	8pm-8:59pm	2			
	9pm-9:59pm			√	250
	10pm-10:59pm				
	11pm-11:59pm			√	150

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 1 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 2 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 3 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

1 = Damp or a few drops of urine on underwear;

2 = Wet your underwear or pad;

3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 4 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 5 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 6 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 7 of 7 DAY DIARY

Visit # _____

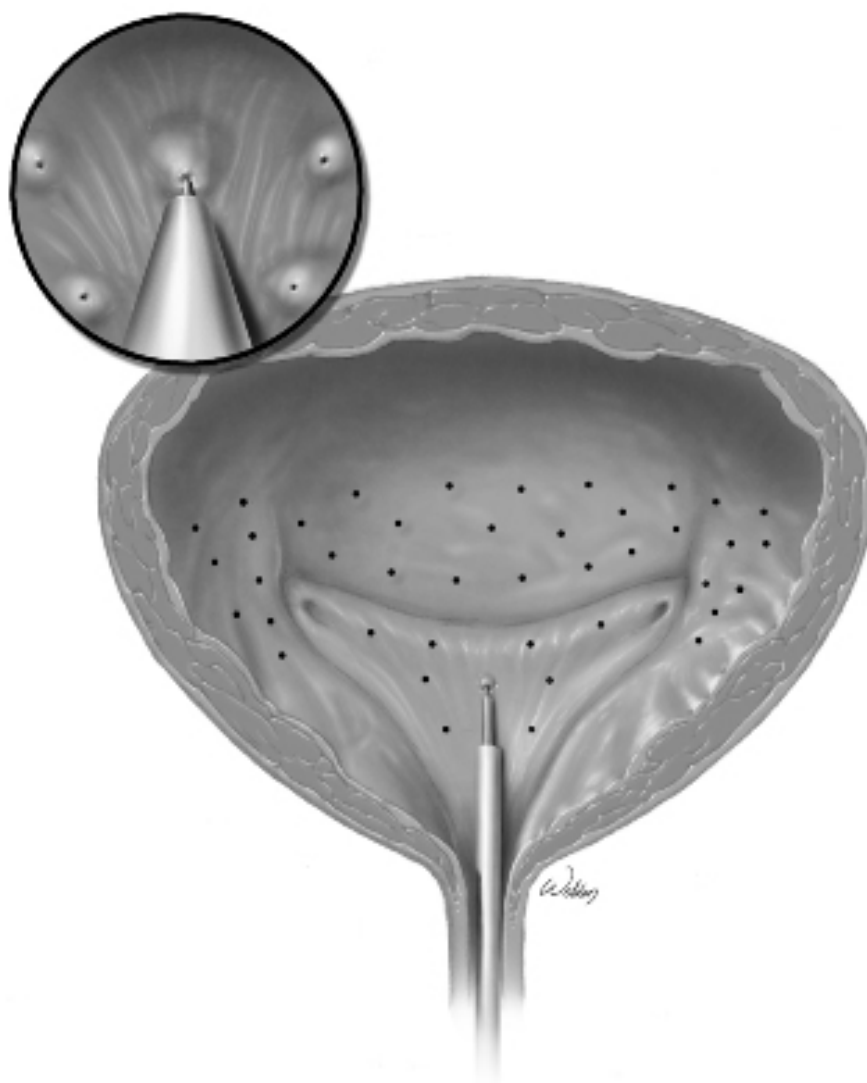
DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

APPENDIX IV

INJECTION DIAGRAM

INJECTION DIAGRAM



The investigator will receive 4 identically appearing syringes pre-filled with 8 mL each of reconstituted study medication (total of 32 mL) from the independent reconstitutor. The first syringe should be attached to the injection needle. 2 mL of study medication should then be used to prime the needle (resulting in a volume of 6 mL in the first dosing syringe). A total of 30 mL remains between the 4 injection syringes for study treatment administration. Each treatment session will be administered as 20 injections each of 1 mL (10u/ml), evenly distributed into the bladder. The injection needle can then be inserted into the injection port of the cystoscope for detrusor injections. Under direct visualization, injections should be distributed evenly across the detrusor walls and dome, spaced approximately 1 cm apart to include the trigone. The needle should be inserted approximately 2 mm into the detrusor for injections. The entire 30 mL will be administered as 30 injections each of 1 mL (total volume administered is 30 mL), evenly distributed into the detrusor via cystoscopy (see Injection Pattern Diagram in Appendix II). After the injections are given, the saline used for bladder wall visualization should be immediately drained. Indwelling catheters may be used during the 24-hour post-treatment period at the discretion of the investigator.

APPENDICES V

QUESTIONNAIRES

H-34972: A Multicenter, Double-Blind, Randomized Study of the Safety and Efficacy of OnabotulinumtoxinA (ONAb_oNT-A) versus Oral Oxybutynin in Spinal Cord Injured Patients with Neurogenic Detrusor Overactivity (Protocol Number 11-09-10-04)

Protocol Changes from 3/15/17 to 5/11/15

Volunteers are no longer required to stop their anticholinergic medication for overactive bladder prior to randomization.

Randomization

Section 6, page 16

Added: Volunteers will be encouraged to washout of medication for 14 days. If they choose to remain on medicine, they will stay on same dose for duration of the study

Inclusion Criteria

Section 7.1, page 16

Revised lower age limit to 15

Exclusion Criteria

Section 7.2, page 18

Deleted: #6.

Informed Consent Process

Section 9, page 19

Added: For children ages 15 through 17 years old, assent will be obtained by adding "If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this, you also note that your child understands and agrees to take part in this study according to his or her understanding." to the adult consent form.

Risk/Benefits Assessment

Section 16.1.2, page 29

Added: If side effects occur, they will be managed as effectively as possible.

A Double-Blind, Randomized Study of the Safety and Efficacy of OnabotulinumtoxinA (ONAbNT-A) versus Oral Oxybutynin in Spinal Cord Injured Patients with Neurogenic Detrusor Overactivity (Protocol Number 11-09-10-04)

Protocol Version: May 11, 2017

PHASE 3B

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KEYWORDS: Botulinum Toxin, Oxybutynin, Overactive Bladder, Spinal Cord Injury, Urinary Incontinence, Nerve Growth Factor, Urine Biomarkers

BCM IRB NUMBER: H-34972 (TIRR Memorial Hermann)

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1. BACKGROUND

1.1 Pathophysiology of Neurogenic Bladder (NGB) due to Spinal Cord Injury (SCI)

Overactive bladder is a condition resulting from disruption of the normal micturition process. It is a syndrome complex characterized by urinary urgency and frequency that may or may not be accompanied by incontinence. Incontinence is due to involuntary contraction of the bladder smooth muscle during bladder filling (detrusor overactivity). [Mills et al, 2000] Neurological disease involving the spinal cord can result in incontinence secondary to a loss of inhibitory input from the micturition center and from interruption of the spinobulbospinal pathways which normally control bladder behavior. The result, demonstrable on urodynamic evaluation, is abnormal involuntary detrusor contractions, often leading to incontinence. In addition, such patients frequently also suffer from urethral sphincters that are unable to relax prior to micturition in a coordinated fashion (i.e. detrusor-sphincter dyssynergia). This lack of coordinated activity can result not only in incontinence but also in vesico-ureteric reflux and/or high storage and voiding pressures which, if left untreated, can lead to potential renal damage. [Foley et al, 1997]

1.2. Epidemiology and Burden of SCI induced NGB

Approximately 10,000 SCIs occur each year, most of which occur in males (80%) [De Vivo et al, 1992]. Many of these patients develop neurogenic bladder dysfunction (NGB) characterized by overactivity of the detrusor muscle, termed neurogenic detrusor overactivity (NDO) or the older term detrusor hyperreflexia (DH). Spinal cord injured patients can also develop detrusor external sphincter dyssynergia (DESD), an abnormal/uncoordinated response of the sphincter to bladder contraction. A combination of these factors can lead to *long-term complications in up to 50% of patients* [Kaplan et al, 1991; McGuire 1979; Yalla et al, 1977]. These complications include hydronephrosis, autonomic dysreflexia, vesicoureteral reflux, nephrolithiasis, sepsis, renal insufficiency or failure and even death. SCI patients often suffer from urinary incontinence which can lead to adverse events such as urinary tract infections and decubitus ulcers, in addition to creating a large care burden for family members or healthcare providers and significantly impairing the veteran's quality of life. Clearly, bladder problems related to SCI have a negative impact not only on patients' physical condition, but also on their emotional and social well-being. Low self-esteem resulting from urinary incontinence can reduce social interaction, depress sexual desire, and interfere with productivity at work, in school, or during rehabilitation of the veteran's primary neurological disease.

1.3. Current Treatment of NGB is Inadequate

Common pharmacologic treatments to reduce bladder contractility include anticholinergics, antispasmodics and tricyclic antidepressants. However, these therapies have limited efficacy and are associated with a high incidence of side effects including dry mouth, constipation and blurred vision [Ouslander, 2004]. A large randomized trial comparing propiverine to oxybutynin in SCI patients found that oxybutynin only reduced daily incontinence episodes by 39%. [Stohrer et al, 2007]. Furthermore, anticholinergic adverse effects were observed in 78% of oxybutynin treated patients in parallel with the limited benefit of the drug in reducing bladder related incontinence. In fact, a large epidemiological study of oral antimuscarinic drug use among NGB patients found that 38% stop therapy within one year of initiation of therapy. [Manack et al, 2011]

Although a large proportion of NGB patients are inadequately treated with standard front-line therapy with oral anticholinergics, up until recently, the only options available to patients who do not respond to or discontinue anticholinergic therapy are invasive procedures such as implantable devices to chronically stimulate the sacral nerve (i.e. limited studies showing utility in NGB patients) or surgical bladder augmentation (i.e. where intestine is harvested and sewn onto the bladder). While these procedures may be effective for some patients, they are highly invasive, expensive, do not necessarily guarantee continence, and may have long term complications [Bosch and Groen, 1998; Bosch, 1998].

1.4. OnabotulinumtoxinA (ONAbNT-A) as an Alternative Treatment of Refractory NGB

Botulinum toxin is a neurotoxin that acts by inhibiting neurotransmitter release from nerve endings. It is commonly used to treat conditions of skeletal muscle spasticity (i.e. cervical dystonia, etc.). In contrast to muscarinic antagonists whose primary beneficial effects are mediated by inhibiting parasympathetic mediated cholinergic transmission to the bladder, ONAbNT-A's denervating effects are widespread. In fact, ONAbNT-A has been shown to inhibit the release of multiple neurotransmitters (i.e. acetylcholine, ATP, norepinephrine) and growth factors (i.e. nerve growth factor, NGF) that depend on SNARE (i.e. soluble N-ethylmaleimide-sensitive factor attachment protein (SNAP) receptor) mediated release from nerve endings. [Abdel-Meguid, 2010] The use of ONAbNT-A in the urinary bladder was first described by Schurch and colleagues who demonstrated a significant increase in mean maximum bladder capacity (296ml to 480ml, $p < 0.016$) and a significant decrease in mean maximum detrusor voiding pressure (65 to 35cm H₂O, $p < 0.016$) in 21 patients with NDO that were injected with ONAbNT-A. [Schurch et al, 2000] A strong impetus driving industry sponsored clinical trials examining the effects of ONAbNT-A on NDO was provided by the first randomized, placebo-controlled trial examining the effects of two doses of ONAbNT-A (i.e. 200 or 300 units) versus saline injection on various parameters including urodynamic measurements and urinary incontinence episodes in patients with refractory NGB resulting from multiple sclerosis (i.e. MS) or SCI. [Schurch et al, 2005] Significant decreases in incontinent episodes (i.e. approximately 50%), significant increases in maximal cystometric capacity (i.e. approximately 170-215ml), and significant improvements in quality of life scores were demonstrated in both ONAbNT-A treatment groups compared to controls. Beneficial effects lasted the duration of the study (i.e. 6 months).

A second double-blind, randomized, placebo controlled study compared the effects of ONAbNT-A (300 U) in 57 patients with urinary incontinence resulting from MS or SCI. At 6 weeks following treatment, ONAbNT-A treated patients demonstrated a 57% reduction in daily incontinence episodes compared to no change in placebo treated patients. [Herschorn et al, 2011] Most recently, a Phase 3 double-blind, placebo-controlled, parallel group study compared the effect of two doses of ONAbNT-A (i.e. 200 U and 300 U) to placebo in 416 patients with urinary incontinence and NDO resulting from multiple sclerosis or SCI and not adequately managed with antimuscarinic medication. At 6 week follow-up, 200 U of ONAbNT-A reduced weekly urinary incontinence episodes by 69%, a significantly greater response than placebo treatment (i.e. 29%). [Ginsberg et al, 2011]

The preceding three randomized studies demonstrate that ONAbNT-A is more effective than placebo for improving the symptoms and signs of NDO, as measured by the reduction in episodes of urinary incontinence as well as improvements in urodynamic parameters. However, in each study **patients were allowed to remain on anticholinergic treatment throughout the duration of the study** so the absolute benefit of ONAbNT-A treatment cannot be assessed.

Moreover, although patients in each study were determined to be refractory to antimuscarinic treatment, the relative effectiveness of antimuscarinic medication versus ONAboNT-A in patients SCI patients suffering from urinary incontinence can only be determined through a randomized, controlled, trial comparing single treatment with either agent.

Finally, prior randomized trials have all excluded bladder trigone injections for fear of inducing vesicoureteral reflux. Studies have disproven this theory and, in fact, mounting evidence suggests that the bladder trigone is an ideal target for ONAboNT-A injections. [Smith et al, 2005; Abdel-Meguid, 2010] For starters, the bladder trigone is densely innervated and contains an abundant concentration of the high-affinity binding site for ONAboNT-A, SV2. [Coelho et al, 2010] Moreover, a recent randomized comparative trial between trigone and non-trigone bladder injection paradigms in patients with SCI induced NDO found that including trigone injections led to significantly greater improvements in urinary incontinence. [Abdel-Meguid, 2010] These findings parallel Dr. Smith and Dr. Chancellor's 14 year personal experience utilizing bladder trigone injections with ONAboNT-A. [Smith et al, 2005]

1.4.1 Use of ONAboNT-A to Treat SCI NGB Patients

We recently reviewed our results using ONAboNT-A in a high-risk population of SCI patients with NGB and decreased bladder compliance. Loss of detrusor compliance creates high urine storage pressure in the bladder with consequent risks to renal function. Data were collected from 24 patients with urinary incontinence secondary to SCI, all of whom underwent intradetrusor injection of ONAboNT-A at The Institute for Rehabilitation and Research (TIRR). [Mengheang et al, 2011] Each patient underwent injection of 300 units of ONAboNT-A, with the exception of one patient who received 100 units.

A total of 24 patients with incontinence of neurogenic origin were included in this study. Mean patient age was 33 years (range 15 to 65), and mean time since SCI was 8.5 years (range 7 months to 24 years). Of the 24 patients, 11 had cervical SCI, 8 had thoracic SCI and 2 had lumbar SCI; the other three patients suffered from transverse myelitis, spinal cord malacia, and cerebral palsy.

Overall, there was significant improvement in urodynamic parameters after ONAboNT-A injection (Table 1).

	Baseline	Follow-up	P value
Compliance (ml/cm H ₂ O)	14 ± 2	29 ± 5	0.002
Maximum cystometric capacity (mL)	322 ± 32	421 ± 33	0.008
Maximum det/ves pressure (cm H ₂ O)	59 ± 4	36 ± 5	<0.001
Reflex detrusor volume (mL)	155 ± 22	187 ± 33	0.37

Table 1. Urodynamic parameters at baseline and follow-up after ONAboNT-A injection

Notably, 22 (92%) of the 24 patients had low baseline compliance, defined as <20 ml/cm H₂O (mean 14 ± 2ml/cm H₂O). In this subset of 22 patients, baseline compliance increased 260% post-treatment, from a mean of 11.2 ± 1 to 29.2 ± 5 ml/cm H₂O, p=0.001 (Figure 2). Seventeen patients (77%) with low baseline compliance had an increase in compliance on follow-up urodynamics.

Furthermore, 18 of the 24 patients had an elevated maximum detrusor pressure (MDP) > 40 cm H₂O with reduction of MDP into the normal range in 9/18 (50%) after ONAboNT-A therapy. Overall, the mean MDP decreased from 59 ± 4 to 36 ± 5 cm H₂O.

Figure 2: A subset of 22 patients with incontinence of neurogenic origin responded to intradetrusor injection of ONAboNT-A with a 260% post-treatment increase of baseline compliance from 11.2 ± 1 to 29.2 ± 5 ml/cm H₂O, p=0.001

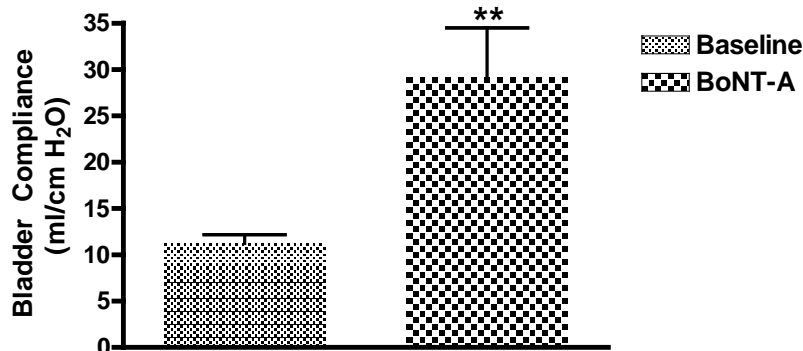


Figure 2. Bladder Compliance

Detrusor overactivity was documented in twenty-three of the 24 patients (96%) during urodynamic study (i.e. documented occurrence of an uninhibited contraction during bladder filling). Post-injection, only 11 (46%) of the 24 patients had uninhibited contractions on urodynamics. There was an increase in reflex detrusor volume on follow-up urodynamics, but it was not statistically significant.

Favorable clinical response was defined as a decrease in frequency of catheterization and/or absence of incontinence episodes. Eighteen of 24 patients (75%) reported a favorable clinical response as defined above. Of the 12 patients with low baseline compliance that experienced improvement in the normal range, 11 (92%) had a favorable clinical response.

1.4.2 Results

In summary, ONAboNT-A bladder injection can significantly improve objective and subjective parameters in SCI patients with high-risk bladders (i.e. decreased bladder compliance). In addition to prior clinical publications between Drs. Smith and Chancellor, [Smith et al, 2005] this data establishes these investigators as clinical experts in the application of ONAboNT-A to patients with urinary incontinence and NGB.

1.5. Urinary Biomarkers in Bladder Dysfunction

Existing therapeutic outcome measures for NGB patients heavily rely on subjective impressions of patients leading to high heterogeneity in clinical response to neuromodulation achieved either by pharmacological or physical means. In the studies described for Aim 2, we will test the following hypothesis to substitute a response variable continuous in nature (i.e. urinary biomarkers) in addition to subjective clinical outcome (i.e. change in urinary incontinence episodes). Nerve growth factor (NGF) is a potent neuronal growth factor with nociceptive and inflammatory properties recently shown to be of importance in bladder pathology. NGF is a

target organ derived growth factor that is produced by most organs lining the upper and lower urinary tract following pathologic insult. [Yoshimura, et al, 2006] NGF is known for neuroimmune interactions. NGF and its receptors may also amplify other immunoinflammatory and neuronal pathways contributing to bladder inflammation and leading to symptoms associated with NGB. We have previously demonstrated that urine NGF levels are elevated in various conditions of bladder dysfunction (i.e. interstitial cystitis, NDO) and can be reduced following bladder injection with ONAboNT-A. [Liu et al, 2009a; Liu et al, 2009b] Taken together, our preliminary data indicate that activation of the NGF and a network of chemokines represents a pivotal final pathway that can be used to construct a biomarker panel for analyzing NGB patients and assessing their treatment response to ONAboNT-A or oxybutynin.

Our hypothesis is that immune and neuronal mechanisms integrate to produce neuroimmune responses as an adaptive mechanism responding to SCI. A dense network of sensory nerve fibers is strategically placed just below the bladder epithelial surface so that any change in the urothelial environment may stimulate the release of proinflammatory neuropeptides by chemokines. [Gabella, 1999; Qin et al, 2005] Chemokines are chemotactic cytokines that constitute a large family of secretory proteins with a molecular weight of 7-10 Kd that are expressed by leukocytes and resident tissue cells.[Mortier et al, 2008] Chemokines exert their effect by interacting with G protein-coupled receptors present on glycosaminoglycans that are linked to endothelial cell layers. [Mortier et al, 2008] Recent studies have shown that chemokines may represent a group of neuromodulatory agents that can alter sensory processing in bladder. [Torrence et al, 2007; Yuridullah et al, 2006] Statistics favor that a panel of independent urinary markers composed of NGF and chemokines will be better than sole reliance on a single urine marker as a surrogate of efficacy of ONAboNT-A and oxybutynin treatment.

Studies have shown that cytokines/chemokines and chemokine receptors are not uniquely restricted to inflammation, but are also responsible for autocrine, paracrine and endocrine signaling by non-immune cells in the bladder such as urothelium and detrusor muscle cells. [Bouchelouche et al, 2004; Bouchelouche et al, 2006] Apart from infiltrated mononuclear cells, recent studies demonstrate that bladder inflammation can be amplified by the resident cells themselves in urothelium through the release of chemoattractants for various inflammatory cells. [Billips et al, 2007; Apostolidis et al, 2008; Schwentner et al, 2008] Previous pre-clinical studies in our lab have already shown that inflammatory signaling is reflected by levels of cytokines in biological fluids interacting with inflamed tissue [Tyagi et al, 2009b]. One of the crucial host defense responses is neutrophil migration to injured urothelium that involves a series of complex interactions with molecules in the lamina propria and at the epithelial barrier. [Godaly et al, 2001] The proteins measured in the urine of NGB like chemokine monocyte chemoattractant protein (MCP-1) and NGF have an established biological role in sensitizing afferents and producing symptoms associated with NDO. [Bhangoo et al, 2007] MCP-1 has also been shown to increase afferent excitability by sensitization of TRPV1 receptor on afferents and the mechanosensitive variant TRPA1 receptors [Jung et al, 2008]. The elevated urinary MCP-1 levels in patients with NGB may be responsible for exacerbation of symptoms by increasing afferent nerve excitability through modulation of TRPV1. The relationship of elevated MCP-1 with symptoms can also be explained by the dose dependent inhibition of GABAergic neurons by MCP-1. [Gosselin et al, 2005; Melik-Parsadaniantz and Rostene, 2008] GABAergic transmission is inherently inhibitory in nature and is likely to attenuate nociceptive transmission. [Miyazato et al 2008]

Urinary proteomics is an attractive option for clinical use, as urine is an ideal source for the discovery of noninvasive biomarkers for human diseases. Therefore, urine presents a rich

source of information for bladder diseases. Disease induced changes in urinary proteome can be traced to overexpression of proteins or abnormal shedding from urothelium into urine. [Tyagi et al, 2009a] Chemokines are subdivided into 4 families (CXC, CC, C and CX₃C) based on the relative position and number of conserved N-terminal cysteine residues as well as the absence (CC) or presence of intervening amino acid(s) between the cysteine residues (CXC). The CC and CXC family have more than one of its members that are implicated in inflammatory pathways.

Many studies have examined the urine as a possible source for biomarkers of urogenital disease because urine is in direct contact with the bladder and prostate and the molecular composition of urine can reflect biochemical and pathophysiological changes in the those organs. [Erickson et al, 2002]

Most of the biomarkers currently used in the clinic have emerged from targeted analysis of candidate biomarkers using immunoassays. [Pirtskalaishvili et al, 1999; Kronborg et al, 2007]] By focusing on a limited number of candidate biomarker proteins, assay technologies providing higher sensitivity and dynamic range such as Luminex can be used. Multiplexed immunoassays (i.e. Luminex) have allowed the measurement of biomarkers associated with bladder dysfunction with very low concentrations in urine that could not be measured for full patient cohorts with conventional immunoassays. In the proposed study, urine levels of chemokines and growth factors will be measured by multiplexed immunoassay panel and normalized by urinary creatinine levels.

The best-established microsphere assay system is the Luminex xMap system (Luminex Corp., Austin, TX), incorporating proven time tested technologies: bioassays, solution phase microspheres, and flow cytometry. [Tyagi et al, 2009a] The antibody specificity of multiplex immunoassays offers simultaneous analysis of a set of markers that can form a fingerprint of the patient responding to treatment with improved sensitivity and specificity. Sensitivity and specificity of biomarkers have been found to be potentiated by use of immunoassay panels which include chemokines, cytokines and angiogenic factors. The sandwich format utilized in the bead based assay as in traditional ELISA not only provides higher-specificity but also minimizes cross-reactivity with other urinary proteins.

1.5.1 Utility of Urinary Biomarkers in Bladder Dysfunction

Studies have shown that cytokines and chemokines responsible for autocrine, paracrine and endocrine signaling are also released by non-immune cells in the bladder such as urothelium and detrusor cells. [Bouchelouche et al, 2004; Bouchelouche et al, 2006a; Bouchelouche et al, 2006b] The urinary bladder relies on a broad array of cytokines, chemokines and growth factors to effect biochemical changes within its organ in response to disease and therapeutic intervention. But not all these chemokines/cytokines and growth factors can serve as urinary biomarkers or surrogates of treatment response as they have to fulfill the key requirement of being present in detectable amounts in urine that can be assayed using standard methods.

For example, although tumor necrosis factor (i.e. TNF) - α is the initiator of the inflammation process in the bladder, it is unlikely to serve as a urine marker for bladder inflammation [Billips et al, 2007; Bouchelouche et al, 2006a], because of its very small amount released into the urine. [Sadeghi et al, 2005] It is quite possible that released TNF- α binds with receptors in surrounding tissue such that only trace amounts are leaked into the urine. Thus, the release of cytokines and other inflammatory mediators into the urine is critical for their utility to serve as a biomarker. With the availability of reliable analysis methods based on immunoassays such as

ELISA, numerous studies have used cytokines as biomarkers in the diagnosis and prognosis for a host of diseases. [Parekattil et al, 2003; Parikh et al, 2006; Rovin et al, 2005; Segerer and Nelson, 2005; Mehta, 2006]

In contrast to urine levels of TNF- α in NGB patients, the detectable amount of NGF in the same patients combined with its known role in neuroimmune interactions makes NGF an ideal candidate for a urinary biomarker. A role for NGF in the development of UTI is not well elucidated and the aims of our preliminary study were to investigate the secreted levels of NGF in urine from symptomatic UTI patients in comparison to patients with asymptomatic bacteriuria (ASB) in SCI patients. Our hypothesis is that immune and neuronal mechanisms integrate to produce neuroimmune responses to ward off UTI, but not ASB. Therefore, changes in urinary NGF levels will reflect the status of the host immune response in lower urinary tract, whether related to ASB or UTI. NGF and its receptors may also amplify other immunoinflammatory and neuronal pathways contributing to bladder inflammation and symptoms associated with UTI.

1.5.2 Elevated Urine NGF Levels in Spinal Cord Injured Patients with Urinary Tract Infection (UTI) but not Asymptomatic Bacteriuria (iASB)

Table 2. Urinary NGF levels in 18 SCI patients.

Time	Urine samples	Urinary total NGF (pg/ml)	Urinary NGF/Cr	Statistics
Baseline ASB	18	4.6 \pm 1.5	0.1 \pm 0.1	
Week 1				
1. ASB and non UTI	13	8.3 \pm 2.1	0.2 \pm 0.1	$p=0.01^*$
2. Symptomatic UTI	5	77.8 \pm 17.3	1.1 \pm 0.5	$p=0.79^\#$
Week 2				
1. ASB and non UTI	9	5.1 \pm 1.8	0.1 \pm 0.1	$p<0.01^*$
2. Prev. symptomatic UTI treated with ABX and now asymptomatic	5	12.8 \pm 8.8	0.2 \pm 0.2	$p=0.04^{**}$
3. New onset Symptomatic UTI	4	85.6 \pm 42.2	1.3 \pm 1.0	$P= 0.75^{**}$

* comparison of urinary NGF/Cr level between the control and disease condition,

comparison of NGF/Cr level between baseline and time point, ** comparison between treated and post-treatment

A pilot study of 18 SCI men at an inpatient spinal cord injury center was carried out. The patients enrolled in the study were at their initial hospitalization after suffering from SCI due to: motor vehicle accidents 11, fall 4, diving 2, and work accident 1. Ten patients were paraplegic and 8 were quadriplegic with a mean age of 38.4 \pm 19 years old. All patients had indwelling catheters during their initial spinal shock phase and all patients demonstrated a positive urine culture (i.e. $>10^5$ colonies/cc). Twelve cultures grew out E. Coli, two cultures grew Staphylococcus aureus, three cultures grew Pseudomonas aeruginosa, and one culture was positive for Klebsiella. None of the men had a history of recurrent UTI's, incontinence, lower urinary tract symptoms, or renal dysfunction prior to SCI, except for one patient that had a renal calculus which passed spontaneously 4 years earlier and another patient that was a Type-2 diabetic.

Sample Purification: Urine was collected from the catheter by nurses from consented patients and an aliquot of urine specimens was sent immediately for urine culture. The remainder of the collected urine samples was immediately placed on ice to prevent degradation by endogenous proteases. Urine was centrifuged for 5 min at 10000 x g to remove cell particles and supernatants were passed through 0.34 mm Whatman chromatography paper. Filtrates were divided into aliquots and transported immediately to the -80°C freezer or maintained at 4°C until transported to the freezer within 4 hours. After removal of cell debris and nuclei, the supernatants underwent microscopic examination with a hemacytometry counting chamber to verify absence of cells or particles.

Using traditional ELISA technique, we investigated the levels of NGF in the urine of ASB and UTI patients. The samples were assayed in triplicate by antigen capture ELISA (Promega, Madison, WI) according to the manufacturer's instructions. The results as shown in Table 2 noted a significant five fold elevation of normalized NGF in UTI versus ASB patients. This was confirmed on two separate group of patients at one and two weeks post catheterization with development of UTI symptoms including new onset of urine leakage around catheter (n=4), new onset bladder spasm (n=4), fever (n=2), and increase in WBC count to above normal range (n=3). A greater than 5 fold elevation of NGF in the urine of UTI patients relative to ASB indicates that NGF is an important mediator of host response towards infection. Moreover, oral antibiotic treatment of five patients with symptomatic UTI for one week significantly decreased the elevated urine NGF relative to values obtained before antibiotic treatment. These results suggest that neuronal mechanisms are important in UTI and subsequent symptoms of urinary frequency. Urinary tract induced release of NGF is likely to lead to short and long term changes in the distribution and reactivity of sensory nerves across the lower urinary tract, promoting exaggerated inflammatory reactions during and after the infection.

On the basis of these observations, we postulate that changes of neurotrophin expression such as NGF in the lower urinary tract may represent an opportunity to separate ASB from UTI. In summary, a biomarker panel developed using a combination of NGF and selected chemokines can be a useful measure in differential diagnosis of UTI versus ASB. It can also be useful as a prognostic indicator of bacteriuria invasion of bladder wall with development of bladder inflammation response that may help judicious use of antibiotic therapy and curb the menace of bacterial resistance.

1.5.3 Urine Chemokine and Growth Factor Levels in Neurogenic Bladder Patients

In a different set of 13 patients with NGB collected from a different clinical site, with a history of SCI or other neurological diseases like MS or diabetes, we analyzed urinary chemokines and growth factors in addition to NGF in a single time point urine specimen, processed similar to NGF analysis above. We were able to consistently detect the following proteins in the urine of these patients: interleukin IL-5, IL-6, IL-1Ra, sIL-2R α , CC chemokines including MCP-1, MIP-1 β , RANTES(Regulated upon Activation, Normal T Expressed and Secreted), CXC chemokines including GRO- α / CXCL1, IL-8, and IP-10 and growth factors including vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet derived growth factor (PDGF-AA), VEGF, PDGF, and NGF (Figure 3). [Jacobs et al 2010]. The detected proteins were part of a screen composed of 32 proteins. Levels of urinary proteins were normalized to the concentration of creatinine (Cr). We will target these proteins to evaluate the effect that ONAbNT-A or oxybutynin ER has on their expression in urine. The selected proteins can be categorized as:

Afferent sensitizers: NGF, MCP-1, IP-10

Pro-inflammatory chemokines/ cytokines: IL-5, IL-6, GRO-a, IL-8, RANTES, MIP-1b,

Angiogenesis mediators: VEGF, PDGF

Ant-inflammatory Proteins: IL-1RA, sIL-2Ra

1.5.4 Changes in Urine Biomarker Levels with Treatment

To demonstrate our ability to detect treatment related changes in urinary proteins, we present data gathered from our pilot study in patients with another model of bladder dysfunction (i.e. interstitial cystitis/painful bladder syndrome (IC/PBS)) implanted with the InterStim® neuromodulator. In contrast to neuromodulation achieved by pharmacological method (ONAbNT-A), the neuromodulation of IC/PBS patients was achieved by physical means using electrical stimulation of afferent nerve fibers by calibrated frequencies of an implanted neurostimulator device (i.e. InterStim®). IC/PBS patients recruited for the study had symptoms of urinary urgency and frequency and bladder pain for at least 3 of the 6 months immediately before the first visit. Enrolled patients had O'Leary-Sant Interstitial Cystitis Symptom Index (i.e. ICSI) and Interstitial Cystitis Problem Index (i.e. ICPI) scores of 20 or higher and patients with pelvic mass, pelvic prolapse, urinary retention, and pelvic malignancies as revealed by physical examination were excluded. Clean catch midstream urine specimens was obtained from patients at baseline (prior to implant of interstim) and at 4, 12, and 24 weeks after implant. Enrolled patients also provided ICSI and ICPI scores at each time a urine specimen was collected. Urine samples were collected in 50ml conical tubes and then centrifuged for 10 minutes at 5,000 x g to remove cells as sediment. Supernatant was removed and divided into 1.5 ml aliquots (cryotubes) and transported immediately to the -80°C freezer or maintained at 4°C until transported to a -80°C freezer within 4 hours. The technique used to measure urinary proteins is illustrated in figure 4.

The decline in urinary chemokines of IC/PBS patients with InterStim treatment correlated with decreased ICSI scores suggesting that symptomatic improvements in a patient's condition measured by the subjective scale of ICSI score was associated with objective measures of temporal changes in urinary levels of chemokines and growth factors. It was clearly apparent that IC/PBS disease is heterogeneous in nature and the patients' respond differently to the same degree of neuromodulation. Variable patient response to electrical as well as to chemical neuromodulation (i.e. injection of botulinum neurotoxin) emphasizes the need for personalized objective monitoring of patients subjected to these treatments using biomarkers.

In summary, use of a multiplexed immunoassay panel (Luminex xMap system) demonstrates its utility in serving the stated objectives of this proposal. The antibody specificity of multiplex immunoassay offers simultaneous analysis of a set of markers that can form a fingerprint of a patient responding to treatment with improved sensitivity and specificity. Multiplexed immunoassays (Luminex) have allowed the measurement of biomarkers associated with bladder dysfunction with very low concentrations in urine that could not be measured for full patient cohorts with conventional immunoassays. These techniques also allow simultaneous evaluation of multiple biomarkers in microlitre volumes of urine sample.

2. STUDY DRUGS

2.1. ONAbNT-A (onabotulinumtoxin A, Botox®, Allergan Inc., Irvine, CA)

ONAbNT-A will be the active formulation. Each vial of ONAbNT-A Purified Neurotoxin Complex, Formulation No. 9060X, contains: 100 units (U) of *Clostridium botulinum* toxin type A,

0.5 mg albumin (human), and 0.9 mg sodium chloride in a sterile, vacuum-dried form without a preservative. One U corresponds to the calculated median lethal intraperitoneal dose (LD50) in mice. A 0.9% sterile saline (without preservative) for injection will be used as diluent for ONAboNT-A.

The ONAboNT-A treatment will be administered once as 20 injections each of 1 mL (10U/ml), evenly distributed into the bladder.

Side Effects: ONAboNT-A: It is expected that some participants may have some or all of the following side effects when given ONAboNT-A. Other side effects may occur which were not seen before. Side effects are usually temporary and manageable. However, it is possible they could cause serious disease or death. The study may include risks that are unknown at this time.

Based on the results of the experimental testing in animals, there may have an increased risk of development of bladder stones.

There have been rare reports of serious and/or immediate or even deadly abnormally sensitive reactions after treatment with ONAboNT-A. These reactions include allergic reaction, skin rash, itching, swelling, and difficulty in breathing.

It is a rare possibility that the injection of ONAboNT-A could lead to botulism. The classic symptoms of botulism include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. The doctor's examination may reveal that the gag reflex and the deep tendon reflexes like the knee jerk are decreased or absent.

There have been rare reports of sudden death, sometimes associated with difficulty in swallowing or pneumonia. There have also been rare reports of heart problems (including irregular heartbeats and heart attack, some resulting in death). Some of these patients were already at risk for heart disease. It is not known if ONAboNT-A actually caused these problems.

It should not be used when infection is present at the injection site or in people known to be abnormally sensitive to ONAboNT-A.

The following events have been observed since it has been marketed: skin rash, itching, and allergic reaction. In general, these side effects occur within the first week following injection and, while usually temporary, they may last several months. Pain, tenderness, or bruising around the injection site may also occur. Local weakness of the injected muscle(s) is expected. Weakness of nearby muscles may also occur due to spread of ONAboNT-A.

ONAboNT-A contains albumin, which comes from human blood. Although the blood is rigorously tested, there is an extremely remote risk for the transmission of viruses and similar infectious agents.

ONAboNT-A placebo (saline) will be the control formulation.

2.2. Oxybutynin Chloride ER (Ditropan XL[®], Teva Pharmaceuticals USA, Sellersville, PA)

Oxybutynin Chloride ER in a 10 mg capsule will be taken twice daily for the course of the study.

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (anti-nicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that Oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Common Side Effects: Blurred vision; constipation; diarrhea; dizziness; drowsiness; dry eyes, nose, skin, or mouth; headache; indigestion; nausea; runny nose; stomach pain or upset; trouble sleeping; weakness.

Severe Side Effects: Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); confusion; difficult or painful urination; fast or irregular heartbeat; fever; hallucinations; mental or mood changes (e.g., agitation); seizures; swelling of the hands, ankles, or feet; vision problems.

Oxybutynin chloride is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin chloride is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

The concomitant use of Oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

The safety of Oxybutynin chloride administered to women who are or who may become pregnant or are breastfeeding has not been established. Therefore, Oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Placebo oxybutynin will be compounded to match the oxybutynin.

The study drugs, ONAboNT-A, ONAboNT-A placebo, Oxybutynin, Oxybutynin placebo will be prepared for randomization by investigational pharmacy. The pharmacy will maintain the drug accountability, perform the randomization, and provide the study drugs to the PI. At the completion of the study, the pharmacy will dispose of unused drug per their standard operating procedures.

3. PURPOSE

This purpose of this clinical research study is to evaluate the safety and efficacy of 200 U ONAboNT-A injected into the detrusor versus oral oxybutynin for the treatment of urinary incontinence (UI) caused by neurogenic detrusor overactivity (NDO) in spinal cord injured volunteers. At baseline and each follow-up period, urine will be collected for analysis of biomarkers for nerve growth factor (NGF) and chemokines/cytokines to determine the potential role of urine biomarkers as patient selection and surrogate endpoints of treatment outcome predictors.

4. STUDY DESIGN

This will be a Phase 3B, double-blind, randomized, placebo-controlled, parallel-group study to assess the safety and efficacy of ONAboNT-A or 10 mg twice a day of oral oxybutynin hydrochloride ER in spinal cord injured volunteers diagnosed with neurogenic detrusor overactivity.

5. STUDY POPULATION

A total of 36 volunteers will be recruited for this study. Volunteers will include both males and females with spinal cord injuries who are 18 to 80 years of age and diagnosed with neurogenic detrusor overactivity. The volunteers will be patients at TIRR Memorial Hermann in Houston, TX. There are no eligibility restrictions as to race or ethnicity.

6. RANDOMIZATION

Volunteers will be randomized using a blocked randomization approach designed by the statistician and implemented by the investigational pharmacy: ARM 1: ONAboNT-A 200 U bladder injection and placebo oral capsule daily or ARM 2: Placebo bladder injection (saline) and oxybutynin ER 10mg capsule twice daily. Subjects will be randomized into one of the two treatment arms, using a block size of 4. The order in which the treatments are assigned in each block is randomized and this process is repeated for consecutive blocks of subjects until all subjects are randomized. This process ensures that after every fourth randomized subject, the number of subjects in each treatment group is equal. Volunteers will be encouraged to washout of medication for 14 days. If they choose to remain on medicine, they will stay on same dose for duration of the study

7. ELIGIBILITY CRITERIA:

7.1. Inclusion

To be included in the study, volunteer must meet the following criteria at screening and Randomization/Day 1:

1. Volunteer is male or female, aged 15 to 80 years old.
2. Volunteer weighs at least 50 kg (110 lb) or more.
3. Written informed consent has been obtained.
4. Written Authorization for Use and Release of Health and Research Study Information has been obtained.

5. Volunteer has urinary incontinence as a result of neurogenic detrusor overactivity for a period of at least 3 months prior to screening as a result of spinal cord injury determined by documented patient history.
6. Spinal cord injury volunteers must have a stable neurological injury occurring at least 6 months or more prior to screening.
7. Volunteer has detrusor overactivity (defined as a phasic rise in bladder pressure during the filling phase determined by urodynamics) demonstrated during the screening period or within 1 year of screening.
8. Volunteer is able to complete study requirements including bladder diary completion and attend all study visits (telephone and clinic), in the opinion of the investigator.
9. Volunteer has a negative pregnancy result if female and of childbearing potential.

The following criteria are also required for entry into the study at Randomization/Day 1:

10. Volunteer experiences at least 14 episodes or more of urinary incontinence per week, including urinary incontinence between scheduled intermittent catheterization, with no more than 2 incontinent-free days, determined by completion of bladder diary during the screening period.
11. Volunteer currently uses or is willing to use clean intermittent catheterization (CIC) to empty the bladder (indwelling catheter is not permitted). Volunteers currently on CIC should be willing to maintain an established CIC frequency throughout the study. Caregiver may perform CIC.
12. Volunteers with a negative urine culture result must take an antibiotic medication for 3 days immediately prior to Randomization/Day 1, on Randomization/Day 1, and agree to continue antibiotic medication for at least 3 days following treatment. Volunteers with a positive urine culture result indicating urinary tract infection (UTI), must take an antibiotic to which the identified organism is sensitive for at least 3 days immediately prior to Randomization/Day 1, on Randomization/Day 1, and continue for 3 days following the procedure (or longer as needed). Antibiotics should be taken for at least 7 days. A UTI is defined as either a positive urine culture result with a bacteriuria count of more than 10^5 CFU/mL conjoint with a leukocyturia more than 5/hpf at screening with urinary tract symptoms or a positive urine culture that, in the investigator's opinion, requires antibiotic therapy.

7.2. Exclusion

Volunteers will be excluded from the study for any of the following criteria at screening or Randomization/Day 1:

1. Volunteer has history or evidence of any pelvic or urological abnormalities including but not limited to the following:
 - elevated serum creatinine more than 2 times the upper limit of normal (reference range)
 - current or history of hematuria, 1) if the hematuria is determined to be a pathologic condition or 2) is uninvestigated
 - interstitial cystitis in the opinion of the investigator

- bladder stones within 6 months of screening
 - surgery or bladder disease other than detrusor overactivity that may impact bladder function with the exception of surgeries for bladder stones (more than 6 months) and stress incontinence, uterine prolapse, rectocele, or cystocele (more than 1 year) from screening.
2. Volunteer has had previous or current botulinum toxin therapy of any serotype for any urological condition within 9 months.
 3. Volunteer has a significant stress component to their urinary incontinence (i.e. stress urinary incontinence) in the opinion of the principal investigator.
 4. Volunteer has a history of narrow angle glaucoma that would preclude use of antimuscarinic medication.
 5. Volunteer has been immunized for any botulinum toxin serotype.
 6. Volunteer has a history or current diagnosis of bladder cancer or has urine cytology results which may indicate bladder cancer not ruled out by investigator at Randomization/Day 1. Suspicious urine cytology abnormalities require the investigator's assessment to ensure that the findings are not indicative of malignancy.
 7. Volunteer is male with previous or current diagnosis of prostate cancer PSA level > 10.0 ng/mL. Volunteers with a PSA level equal to or greater than 4.0 ng/mL and equal to or less than 10.0 ng/mL must have prostate cancer ruled out to the satisfaction of the investigator according to local site practice. PSA age to be checked is on male patients 50 years or older, unless has a family history of prostate cancer or is of African American descent then PSA age to be checked is at age 40 years old.
 8. Volunteer has 24 hour total volume voided/catheterized more than 3000 mL of urine determined by completion of bladder diary collected over one consecutive 24 hour period during the 7 day diary collection period prior to Randomization/Day1.
 9. Volunteer has an active genital infection, other than genital warts, either concurrently or within 4 weeks prior to screening.
 10. Volunteer uses any anti-platelet or anticoagulant therapy or is using medications with anticoagulative effects within 3 days prior to treatment. Some medications may need to be withheld for more than 3 days per clinical judgment of the investigator.
 11. Volunteer has hemophilia or other clotting factor deficiencies or disorders that cause bleeding diatheses.
 12. Volunteer has had concurrent treatment or treatment within 6 months of Randomization/Day 1 with capsaicin or resiniferatoxin.
 13. Volunteer is currently using or plans to use an implanted or non-implantable electrostimulation/neuromodulation device for treatment of overactive bladder.
 14. Volunteer has a known allergy or sensitivity to any components of the study medication, anesthetics or antibiotics or any other products associated with the treatment and general study procedures.
 15. Volunteer has any medical condition that may put the volunteer at increased risk with exposure to ONAboNT-A including diagnosed myasthenia gravis, Eaton-Lambert syndrome or amyotrophic lateral sclerosis.
 16. Volunteer is female and pregnant, nursing or planning a pregnancy during the study, or of childbearing potential and unable or unwilling to use a reliable form of contraception during the study.

17. Volunteer is currently or has previously participated in another therapeutic drug or device study within 30 days of screening.
18. Volunteer has any condition or situation which, in the investigator's opinion, puts the volunteer at significant risk, could confound the study results, or may interfere significantly with the volunteer's participation in the study.

8. RECRUITMENT PROCESS

The volunteers will be identified from the Spinal Cord Injury or the Urology Clinic at TIRR Memorial Hermann. They will be initially approached by their spinal cord injury or urology clinic physicians for recruitment into the study. If they wish to participate in this study, they will then be approached by Dr. Smith or his research staff. The study will be published on the BCM clinical trials websites. BCM's site is <http://www.bcm.edu/clinicalstudies/?PMID=7201>. The study will also be listed on ClinicalTrials.gov.

Advertising brochures will be placed in the Urology and SCI Clinics and included in a mail out planned for potential subjects. An advertisement will be placed on the Craig's List website.

9. INFORMED CONSENT PROCESS (See APPENDIX I)

Volunteers will be informed both verbally and in written form of the study and procedures involved and be given adequate opportunity to read it and discuss with family before it is signed. The PI and designated study staff will obtain a signed/dated Informed Consent Document (ICD) before enrolling each volunteer. The original signed/dated ICD will be kept with the research study documents, a copy will be given to the volunteer, and a copy will be placed in the volunteer's electronic medical record. The subjects consented at TIRR will have their ICDs scanned into a Master File located on a server that is managed and protected by the BCM IT department. The BCM's ICD provides a signature line for a volunteer's Legally Authorized Representative if applicable. Each patient executing an informed consent document will be given a unique consecutive number beginning with the number 001.

For children ages 15 through 17 years old, assent will be obtained by adding "If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this, you also note that your child understands and agrees to take part in this study according to his or her understanding." to the adult consent form.

10. STUDY PROCEDURES (See APPENDIX II)

10.1 Screening - Visit 1

After informed consent is obtained, the following will occur at least 2 weeks but not more than 4 weeks prior to randomization/treatment:

- Inclusion/Exclusion criteria
- History and Physical Exam, including vital signs, weight
- Assessment of concurrent medications/procedures
- Kidney ultrasound or results of exam conducted within 1 year of enrollment
- Post void residual (PVR) in volunteers who micturate or have a mixed catheterization/micturition pattern

- Urine specimen to conduct urinalysis, urine culture and sensitivity
- CBC (Complete Blood Count)
- CMP (Complete Metabolic Panel)
- Pregnancy test - serum (for females only)
- Prostate specific antigen (for males only) PSA age to be checked is on male patients 50 years or older, unless has a family history of prostate cancer or is of African American decent then PSA age to be checked is at age 40 years old.
- OAB-Patient Satisfaction with Treatment Questionnaire (OAB_PSTQ)
- Urodynamic studies (if not performed 1 year prior to the Randomization Visit): This procedure measures bladder function. Lubricated catheters with pressure sensors are placed through the urethra into the bladder under sterile conditions and into the rectum.

The volunteer will then be placed in the sitting position and the pressure transducers will be leveled with the pubic symphysis.

The pressures bladder (Pves) and rectum (Pabd) are measured while the bladder is filled with saline at 40ml/min. The urodynamic machine will also record the subtracted detrusor pressure ($P_{det} = P_{ves} - P_{abd}$). Where the Pabd pressure is adjusted at baseline to render $P_{det} = 0$ by manipulation of the amount of fluid in the rectal balloon. The study will be performed following the guidelines of good urodynamics practices from the International continence society [Schafer et al, 2202; Paralyzed Veterans of America/Consortium for Spinal Cord Medicine, 2001].

The volunteer will be asked to perform several maneuvers during the procedure. These include:

- 1) Coughing (or bearing-down) several times during this procedure to make sure the equipment is working properly
- 2) Trying to suppress overactive bladder contractions, if present with sensation to stop voiding during the contractions.
- 3) To tell the urodynamicist when the bladder is maximally full.

The urodynamic study will take about 20-30 minutes to complete, with about 20 - 30 minutes of additional setup time.

Urodynamic parameters measured are baseline pressure, volume at first involuntary detrusor contraction, Peak detrusor pressure during first involuntary detrusor contraction, Maximum cystometric capacity, end fill pressure at maximum cystometric capacity or at the involuntary detrusor contraction used to determine maximum cystometric capacity and detrusor compliance.

- Volunteers will be instructed to complete a bladder diary for 7 consecutive days prior to next visit (Appendix IV)
- Dispense an antibiotic [Bactrim DS 1 tab twice a day] with instructions to take for 3 days prior to treatment (Day 1), on Day 1, and for 3 days following treatment day (total of 7 days). If subject has an allergy to sulfa or if urine culture indicates Bactrim resistant, another drug may be substituted.
- Volunteers will be instructed to stop taking medications for overactive bladder symptoms two weeks prior to injection.

10.2. Study Procedures/Study Interventions

10.2.1. Randomization and Treatment -Visit 2 (14 days to 6 weeks from Visit 1)

Volunteers will be reviewed for eligibility criteria. The following assessments will take place prior to randomization:

- Vital signs
- Urine Pregnancy test (for females only). If positive, a serum pregnancy test will be conducted to confirm.
- Urinalysis
- Post void residual in volunteers who micturate or have a mixed catheterization/micturition pattern
- Confirmation that overactive bladder medications were not taken 2 weeks prior to this visit.
- Assessment of concurrent procedures/medications, and adverse events
- Review of bladder diary
- Antibiotic drug accountability to assess compliance in taking of antibiotics

Volunteers will then be randomized to one of the two treatment groups. The following activities will take place prior to treatment:

- Urine collection for biomarker assessment
- Incontinence Quality of Life Instrument (I-QOL) and Incontinence Quality of Life Instrument (I-QOL) neurogenic module questionnaires will be completed. (See APPENDICES V-VIII: Questionnaires)

After randomization, the following events will occur:

- Bladder injection (with ONAboNT-A or saline) and initiation of oral therapy (with oxybutynin ER or placebo).
- All volunteers will be observed for at least 30 minutes after treatment prior to discharge.
- Volunteers will be instructed to continue oral antibiotics for 3 days.
- All volunteers will be instructed to complete a bladder diary for 7 consecutive days in the week prior to next visit.

10.2.1.1 Injection Procedures

10.2.1.1.a. Treatment Allocation, Use and Preparation

Volunteers will receive either ONAboNT-A 200 U or saline injection according to randomization to treatment sequence. Drug will be reconstituted/prepared by the investigational pharmacist at TIRR.

10.2.1.1.b. Administration

10.1.1.1.b.1. Study Treatment Anesthesia

The use of anesthesia during the injection procedure is determined by the investigator based on the medical need of the volunteer (e.g., tolerance to the procedure, spasticity, risk of autonomic

dysreflexia, etc.). Preventative measures regarding autonomic dysreflexia are permitted per local site practice.

The following options are permitted:

- No anesthesia
- Local anesthesia: instillation of the bladder with 1-2% lidocaine (or similar acting agent) for at least 15 minutes in order to achieve sufficient anesthesia in patients with sensate bladders or at risk for autonomic dysreflexia.
- Prior to treatment administration, the bladder should be drained of lidocaine, rinsed with saline and drained again
- Sedation may also be administered according to local site practice if deemed medically necessary
- General anesthesia: general anesthesia may be used according to local site practice by an appropriately qualified anesthesiologist. However, the use of neuromuscular blocking agents is not permitted.

10.2.2. Treatment Procedure

- The investigator should confirm that the volunteer has taken their pretreatment antibiotics as specified.
- Laboratory results must be reviewed and evaluated by the investigator indicating that they were found to be acceptable prior to treatment, including a negative serum pregnancy test for women of childbearing potential. Volunteers should continue to meet inclusion and exclusion criteria.
- Questionnaires must be completed prior to treatment.
- A flexible or rigid cystoscope may be used for study treatment injections. The bladder should be instilled with a sufficient amount of saline in order to achieve adequate visualization for the study injections.
- The investigator will receive 2 identically appearing syringes pre-filled with approximately 10 mL each of reconstituted study medication (200 U of ONAboNT-A in 20ml of preservative free saline or 20 ml preservative free saline) from the independent reconstitutor. The first syringe should be attached to the injection needle. The injection needle can then be inserted into the injection port of the cystoscope for detrusor injections. Under direct visualization, injections should be distributed evenly across the detrusor walls spaced approximately 1 cm apart to include the trigone. The needle should be inserted approximately 2 mm into the detrusor for injections. The entire 20 mL will be administered as 20 injections each of 1 mL (total volume administered is 20 mL), evenly distributed into the detrusor via cystoscopy. The injection process will take approximately 15 minutes to complete. After the treatment is finished, the patient will remain in the clinic for at least 30 minutes for observation. Also, he/she will be asked to urinate before leaving the office. If the patient cannot satisfactorily urinate to empty his/her bladder [i.e. urinary retention], a temporary catheter may be used to drain the bladder. (See APPENDIX IX: Injection Pattern Diagram)
- All volunteers must be observed for at least 30 minutes following the study treatment administration. Safety monitoring and assessments are to be done according to local site practice (e.g., monitoring of blood pressure, pulse rate and ensuring that volunteer has emptied the bladder before leaving the site).
- Spinal cord injury volunteers with lesions above the T6 level are particularly at risk of developing autonomic dysreflexia, which presents with symptoms of increased blood

pressure, relative bradycardia, headache, and skin flushing [Blackmer, 2003]. Should autonomic dysreflexia develop in a volunteer, the condition should be immediately handled according to local site practice. An occurrence of autonomic dysreflexia during study drug administration will be reported as an adverse event. Guidelines for managing autonomic dysreflexia will be included in the Investigator Binder [Paralyzed Veterans of America/Consortium for Spinal Cord Medicine, 2001].

- Volunteers should be instructed to contact the study site if they experience any adverse events post-treatment.

10.3 Post Randomization/Treatment Visits (Follow Up) -Day 3, and Weeks 4, 12, and 24 (\pm 3 days) post randomization/treatment

10.3.1 Visit 3: Day 3 to 5 post randomization/treatment (Telephone Visit)

Discuss subject's well-being, concomitant medications, antibiotic compliance, and side-effects or adverse events.

10.3.2 Visits 4: Week 4 (\pm 3 days) post randomization/treatment

- Vital Signs
- PVR for volunteers who micturate or have a mixed catheterization/micturition pattern
- Urine collection for biomarker assessment
- Urinalysis, culture and sensitivity
- Collect bladder diary for Total Volume Voided assessment
- Collect oral study drug pill bottle.
- Urine pregnancy test (females). If positive, a serum pregnancy test will be conducted to confirm.
- Concurrent medications and procedures
- Adverse events assessment
- The I-QOL), (I-QOL) neurogenic module, OAB-Patient Satisfaction with Treatment Questionnaire (OAB_PSTQ), and Patient Global Assessment (PGA) questionnaires will be completed.
- Volunteer will be instructed to complete a bladder diary for 7 consecutive days in the week prior to next visit.
- Dispense oral study medicine with instructions to bring all unused medicine to next visit.

10.3.3. Visit 5: Week 12 (\pm 3 days) post randomization/treatment

- Same events and procedures as previous study visits plus urodynamic studies.

10.3.4. Visit 6: Week 24 (\pm 3 days) post randomization/treatment - End of Study Visit

- Physical Exam, including vital signs
- CMP (Complete Metabolic Panel)
- PVR for volunteers who micturate or have a mixed catheterization/micturition pattern
- Urine collection for urinalysis, culture and sensitivity, and biomarker assessment
- Study drug accountability
- Collect bladder diary

- Serum pregnancy test (females)
- Concurrent medications and procedures
- Adverse events assessment
- Questionnaires = I-QOL, I-QOL-Neurogenic Module, OAB-PSTQ, PGA

11. SAMPLE SIZE JUSTIFICATION

Data from a preliminary study in SCI patients showed that Ditropan XL (i.e. oxybutynin ER equivalent) reduced weekly urinary incontinence episodes at 12 weeks by 54% (i.e. from 13 to 6 per week).[Bennett et al., 2004] A second large randomized trial found that oxybutynin lowered incontinence episodes from 3.3 to 2 (i.e. 39%) after 21 days of treatment.[Stohrer et al, 2007] The most recent and largest efficacy and safety study demonstrated that ONAboNT-A reduced weekly urinary incontinence episodes by 69% at 6 weeks (i.e. from 30.5 to 9.5 per week). [Ginsberg et al, 2011] Our patient population will consist of patients having a relatively high number of weekly urinary incontinent episodes, similar to those in the Ginsberg study. Although our study groups will include a placebo pill and sham injection group we don't expect to see a significant placebo effect in our neurogenic bladder population as has been previously demonstrated in idiopathic (i.e. non-neurogenic) overactive bladder populations. For this study, we will assume a reduction of 69% in incontinence episodes for the ONAboNT-A group and a 45% reduction in the oxybutynin group (i.e. a value midway between the results of Bennett et al, 2004 and Stöhrer et al, 2007).

Our sample size assumptions include a mean baseline level of 30 weekly incontinent episodes, a 69% reduction of incontinent episodes in the ONAboNT-A + placebo pill group (i.e. post-treatment 9 incontinent episodes), a 45% reduction in the oxybutynin + sham injection group (i.e. post-treatment 17 incontinent episodes) at 12 weeks, an alpha level of 0.05, 80% power and a standard deviation of 50% of the mean. The resulting sample size of 18 subjects per group (total=36) is adjusted for an expected attrition of 20%. This effect was selected as the smallest effect that would be important to detect, in the sense that any smaller effect would not be of clinical or substantive significance. It is also assumed that this effect size is reasonable, in the sense that an effect of this magnitude could be anticipated based on previous findings.

12. DATA ANALYSIS

Initially, graphical methods will be used to assess distributional properties of the data (weekly urge incontinent episodes, urine biomarker levels, quality of life scores) and to examine patterns of correlations between observations at different time points. Measures such as age, gender, number of weekly urinary incontinence episodes, urine biomarker levels, I-QOL and I-QOL neurogenic questionnaires and disease severity will be examined using summary statistics to determine if any baseline differences exist between the 2 study groups. If extreme departures from normality are found, non-parametric methods such as the Wilcoxon rank-sum test or transformation of the data will be considered. Questionnaire scores will be examined for reliability using Cronbach's alpha. The distributions of the scores will be examined to see if they are evenly distributed around the mid-point of the scales or are clustered at the top or bottom of the scales (ceiling or floor effect). If strong ceiling or floor effects are found, this could limit the usefulness of these measures.

The primary endpoint is the reduction in mean weekly incontinent episodes in the ONAboNT-A treated group compared to the oxybutynin treated group at 12 weeks. The change between the 2 groups at 12 weeks will be analyzed using a general linear model approach with weekly

urinary incontinent episodes as the outcome variable, treatment group as the independent variable with adjustment for baseline weekly urinary incontinent episodes, a baseline covariate. This approach is equivalent to the independent t-test, but allows adjustment for the baseline outcome levels. Exploratory growth curve analysis will be done to investigate the pattern (linear, quadratic or possibly cubic) of change in incontinence episodes over time during the entire data collection period. Growth curve models have an assumption for multivariate normality of the dependent variables. If the data are not normally distributed but approximately follow some exponential distribution, then a generalized linear model using a generalized estimating equation can be applied. The generalized estimating equation links functions to allow maximum likelihood estimation for variables that follow a distribution from the exponential family other than the normal. [McCullagh and Nelder, 1989] The same hypotheses can be tested with these methods as with the normal growth curve model.

Secondary endpoints, such as quality of life scales, will be tabulated using cross tabulations and summary statistics. Measures of association such as chi-square and correlations will be used to assess differences in relationships between the control and intervention groups. Changes in these secondary measures between control and intervention groups at 12 weeks will be compared using independent t-tests or the Wilcoxon rank-sum test. Additionally, we will look at the longitudinal pattern of the questionnaires at baseline, 4, and 12 weeks using growth curve modeling to explore the trajectory of change. Statistical analysis will be done using SAS, version 9.2 software.

13. ENDPOINTS

The **Primary Endpoint** is the mean reduction in weekly incontinence episodes 12 weeks following treatment. **Secondary Endpoints** include improvements in quality of life scales (Incontinence Quality of Life Instrument (I-QOL), Incontinence Quality of Life Instrument Neurogenic Module, OAB-Patient Satisfaction with Treatment Questionnaire (OAB_PSTQ), and Patient Global Assessment (PGA), changes in maximum capacity by urodynamic study, as well as reductions in urine NGF and chemokine/cytokine levels (pg/ml normalized to creatinine). We will also correlate NGF and chemokine/cytokine levels with disease severity and treatment outcome. Other endpoints include detrusor compliance (DC) (ml/cm H₂O) by urodynamics, total volume voided recorded over one 24 hour period as recorded on bladder diary for all voids (catheterization and voluntary), and number of episodes per day of voiding and method (catheterization and voluntary) as recorded by bladder diary, and the frequency of asymptomatic bacteriuria (i.e. ASB) versus symptomatic UTI's. We will correlate NGF and chemokine/cytokine levels with disease severity, the presence of ASB versus symptomatic UTI, and treatment outcome.

14. LABORATORY EVALUATIONS

14.1. Specimens

Urinary levels of NGF, cytokines and chemokines will be measured at study visits 2, 4, 5, and 6. Urine will be collected by sterile catheter or clean catch midstream (CCMS) voided specimen. Specimens will be processed at the time of collection, de-identified with an untraceable number, and shipped to the Urology Research laboratory at William Beaumont Hospital, Royal Oak, MI, under the direction of Michael B. Chancellor, MD. The identification number will be used in research documents.

14.2 Specimen Preparation, Evaluation, and Analysis

The Urology Laboratory Manual (Appendix II) will provide specific information.

14.3. Confidentiality

The data will be stored with Dr. Chancellor in a locked office. Urine will only be identified by volunteer identification number and initials prior to shipping. Dr. Chancellor will not have access to any other patient identifiers. The urine will be placed into a minus 80 freezer in the locked urology research laboratory with restricted access to the Research Institute.

To ensure rigorous HIPPA compliance throughout the study, each urine specimen from the volunteers enrolled in the study will be stored in the urology biobank, which will de-identify the specimens with an untraceable number upon receiving the specimen to delink the volunteer clinical data from analysis team. This number will be used in research documents. All data will be stored in Dr. Chancellor locked office. The key to urine biobank number and volunteer identification number is held in Urology research office accessible only to Dr. Chancellor.

The risks from breach of confidentiality will be minimized by using de-identified volunteer specimens and the secured computer database maintained in the urology biobank will protect the identity of volunteers from the analytic team.

After research testing required for this study is completed, the remaining portion of urine samples will be stripped of the code and will be banked for future use. It will be kept until it is all gone. Samples will not be sold or transferred to anyone else. If at any time the subject withdraws from this study he will not be able to get his urine samples back because there is no identifying information on the samples.

15. DATA COLLECTION AND MANAGEMENT

15.1. Methods for Data Collection

Protocol-specific data will be collected on Case Report Forms and forwarded to the biostatistician for compilation by the data manager. The completed dataset is available to the investigators and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from BCM. (See APPENDIX XI: Case Report Forms)

15.2. Volunteer Identifiers

An unambiguous volunteer identification code will be used in lieu of the volunteer's name on all study data compiled. This volunteer identification code will include the volunteers' initials and volunteer number. A key for this code will be maintained by the Principal Investigator and kept separate from study files. All source documents and study data will be kept confidential. Study data will be kept in a locked file cabinet and/or password protected and encrypted computers and stored on servers managed by BCM IT.

15.3. Confidentiality

15.3.1 Baylor College of Medicine (BCM) and TIRR Memorial Hermann

The PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

Research data will be maintained by Dr. Smith in his office in the Baylor Urology Clinic.

Regulatory documents will be managed by Research Administration of the Scott Department of Urology, BCM located in 502/506D in the Jewish Wing of Main Baylor. The Faculty Center suite utilizes an electronic locking system for security purposes. The Main Baylor offices have keyed entries. All computers utilized for this study are password protected and encrypted. Data is stored on encrypted BCM servers that are managed by IT.

The BCM Scott Department of Urology complies fully with the HIPAA Privacy Rule.

Regulatory authorities that provide oversight of this clinical trial include IRBs, OHRP, and any other applicable state and local authorities will have access to the study data.

15.3.2. William Beaumont Hospital

All specimens will be shipped to the laboratory with only volunteers' initials and volunteer ID# as identifications. Dr. Chancellor will not have access to the key code list of volunteers.

15.4. Disposition of Data

To enable evaluations and/or audits from Health Authorities/BCM, the investigators agree to keep records, including the identity of all participating volunteers (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all CRF's, and detailed records of drug disposition. The requirements of the IRB will also be met.

15.5. Sharing Study Results

Volunteers may never be able to obtain limited research health information.

16. RISK/BENEFITS ASSESSMENT

16.1. Foreseeable Risks:

16.1.1. ONAboNT-A

It is expected that some participants may have some or all of the following side effects when given ONAboNT-A. Other side effects may occur which were not seen before. Side effects are usually temporary and manageable. However, it is possible they could cause serious disease or death. The study may include risks that are unknown at this time.

Based on the results of the experimental testing in animals, there may have an increased risk of development of bladder stones.

There have been rare reports of serious and/or immediate or even deadly abnormally sensitive reactions after treatment with ONAboNT-A. These reactions include allergic reaction, skin rash, itching, swelling, and difficulty in breathing.

It is a rare possibility that the injection of ONAboNT-A could lead to botulism. The classic symptoms of botulism include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. The doctor's examination may reveal that the gag reflex and the deep tendon reflexes like the knee jerk are decreased or absent.

There have been rare reports of sudden death, sometimes associated with difficulty in swallowing or pneumonia. There have also been rare reports of heart problems (including irregular heartbeats and heart attack, some resulting in death). Some of these patients were already at risk for heart disease. It is not known if ONAboNT-A actually caused these problems.

It should not be used when infection is present at the injection site or in people known to be abnormally sensitive to ONAboNT-A.

The following events have been observed since it has been marketed: skin rash, itching, and allergic reaction. In general, these side effects occur within the first week following injection and, while usually temporary, they may last several months. Pain, tenderness, or bruising around the injection site may also occur. Local weakness of the injected muscle(s) is expected. Weakness of nearby muscles may also occur due to spread of ONAboNT-A.

BOTOX contains albumin, which comes from human blood. Although the blood is rigorously tested, there is an extremely remote risk for the transmission of viruses and similar infectious agents.

16.1.2. Oxybutynin ER: Also known as Ditropan XL

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that Oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Common Side Effects: Blurred vision; constipation; diarrhea; dizziness; drowsiness; dry eyes, nose, skin, or mouth; headache; indigestion; nausea; runny nose; stomach pain or upset; trouble sleeping; weakness

Severe Side Effects: Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); confusion; difficult or painful urination; fast or irregular heartbeat; fever; hallucinations; mental or mood changes (e.g., agitation); seizures; swelling of the hands, ankles, or feet; vision problems.

Oxybutynin chloride is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin chloride is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

The concomitant use of Oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects. If side effects occur, they will be managed as effectively as possible.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

The safety of Oxybutynin chloride administered to women who are or who may become pregnant or are breastfeeding has not been established. Therefore, Oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

16.1.3. Placebo

Since placebo has no active drug, the medical condition may become worse, stay the same or improve.

16.1.4. Antibiotics (CIPRO, or generic, 500 mg twice a day)

The most frequent side effects of ciprofloxacin include nausea, vomiting, diarrhea, abdominal pain, rash, headache, and restlessness. Rare allergic reactions have been described, such as hives and anaphylaxis (shock).

16.1.5. Cystoscopy with Bladder Injection

The discomfort is nearly identical to being catheterized, which generally causes slight to moderate discomfort. There will be a feeling of fullness in the bladder and a sensation to empty during the cystoscopy examination. Bleeding, infection, damage to urethra or surrounding structures may occur.

16.1.6. PVR

The risks of having a catheter placed in the bladder for draining the residual urine are infection of the urinary tract, injury to the urethra caused by rough insertion of the catheter, narrowing of the urethra due to scar tissue caused by the insertion of a catheter, injury to the bladder caused by incorrect insertion of the catheter.

16.1.7. Urodynamics

Generally the risks of a urodynamic study are low and are no more than those of a Foley Catheter insertion, which include the possibility of infection, trauma to the urethra or prostate,

traumatic bleeding from the catheterization, discovery of previously unsuspected urethral stricture with inability to get the urodynamics catheter into the bladder.

Patients with a spinal cord injury generally occurring at the Thoracic 5 (T-5) level and above have a risk of experiencing autonomic dysreflexia during bladder filling during the urodynamic or study treatment procedures. To minimize this risk continuous blood pressure monitoring is performed throughout the study.

Autonomic dysreflexia can develop suddenly, and is a possible emergency situation. Symptoms of autonomic dysreflexia include the following: elevation in blood pressure, headache, goose pimples, sweating above the level of injury, nasal congestion, slow pulse, blotching of the skin, and restlessness. If not treated promptly and correctly, it may lead to seizures, stroke, and in some cases, even death.

16.1.8. Ultrasound

Ultrasound testing is painless and harmless but the volunteer might experience anxiety in anticipation of the test. Ultrasound tests involve no radiation and studies have not revealed any adverse effects.

16.1.9. Blood draw

Inserting needles into veins for collecting blood may be uncomfortable. Risks include slight bruising at the puncture site, fainting, the formation of a small blood clot or swelling of the vein and surrounding tissue, bleeding from the site, and the remote possibility of infection at the site of the needle puncture. Fainting is usually harmless, of short duration, and typically produces feelings of weakness, sweating, slowing of the heart rate and an abnormal decrease in blood pressure. Care will be taken to avoid these complications.

16.1.10. Questionnaires

Completing the questionnaires may cause you to have or to experience some level of emotional discomfort due to the personal nature of the questions. The study doctor and staff will maintain a professional and caring attitude while administering the questionnaires.

16.1.11. Confidentiality

The loss of confidentiality regarding research information is a possibility, although, the risk is extremely small. The investigator and his staff will make every effort to maintain the confidentiality.

16.1.12. Pregnancy

It is possible that the medicines used in this study could injure a fetus if volunteer or volunteer's partner becomes pregnant while taking them. Pregnant and/or lactating women will be excluded from the study. As outlined in the protocol, women of childbearing potential will be carefully screened with serum pregnancy testing within 48-72 hours prior to randomization and each treatment (s). Because of the potential risks involved, pregnancy should not occur during participation in this study. The following methods of contraception, if properly used, are generally considered reliable for females of childbearing potential who may participate in the study: oral contraceptives, patch contraceptives, injection contraceptives, male condom with intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring,

intrauterine device, surgical sterilization (bilateral tubal ligation), vasectomized partner(s), or total sexual abstinence.

16.2. Risk Management and Emergency Response

16.2.1. Safety Measures

The following safety measures are included in the protocol in an effort to eliminate risks to volunteers:

- Physical examination
- Vital signs
- Urinalysis
- Urine culture and sensitivity
- Kidney ultrasound
- Post void residual (PVR) by bladder scan, ultrasound, or catheterization for volunteers who micturate or have a mixed catheterization/micturition pattern
- Serum pregnancy test for female volunteers of childbearing potential at screening, qualification for re-treatment if urine pregnancy is positive, and study exit
- Urine pregnancy test for female volunteers of childbearing potential on day of treatment (prior to each treatment). If positive, a serum pregnancy test will be conducted to confirm.
- Concurrent medications
- Concurrent procedures
- Serious medical events
- Adverse events

16.2.2. Health outcome measures

- Incontinence Quality of Life Instrument (I-QOL) [Patrick et al, 1999]: The I-QOL is a disease-specific, quality of life (QOL) questionnaire designed to measure QOL impact of urinary incontinence on volunteers. Designed for self-completion, the I-QOL takes approximately 5 minutes to complete. The I-QOL is scored as a total score, and 3 domain scores of Avoidance Limiting Behavior, Psychosocial Impact, and Social Embarrassment.
- Incontinence Quality of Life Instrument Neurogenic Module [Lee et al, 2005]: The I-QOL Neurogenic Module is designed to measure the impact of urinary incontinence on volunteer's lives in a neurogenic population.
- OAB Patient Satisfaction with Treatment Questionnaire (OAB-PSTQ): The OAB-PSTQ is a volunteer satisfaction with treatment questionnaire created by Allergan, Inc. Volunteers' goals and expectations from treatment are assessed.
- Patient Global Assessment (PGA): The PGA is a global volunteer assessment that assesses the volunteer's symptoms, quality of life, activity limitations and overall emotions.

16.2.3. Stopping Criteria

If moderate to severe adverse events occur after an injection of ONAboNT-A, then no further injection will be given. If moderate to severe adverse events occur due to the Oxybutynin, the medication will be stopped. Volunteers will be symptomatically treated and closely monitored after any moderate to severe adverse events.

In the event of an emergency, the research pharmacy will provide the unblinded information for the volunteer. Care will be provided to the volunteer at the VA Medical facility.

16.3. Potential benefits

Approximately 25 million Americans suffer from varying degrees of urinary incontinence with many of these being caused by neurogenic detrusor overactivity (NDO) in spinal cord injured patients. Antimuscarinic drugs, while effective in many patients, have significant adverse events like dry mouth, constipation, and blurred vision that limit their utility. The potential benefits to the volunteer include improvement in the urinary incontinence symptoms, reduction in the rate of urinary tract infections, decrease in the number of required catheterizations, and an ease of the financial burden of buying protective garments.

The potential benefits to society in addition to those mentioned above would include the decrease in medical costs.

16.4. Intent to benefit

For volunteers that cannot give their own consent to participate in this study, an intent to benefit will be promulgated by the fact that each participant will be given the opportunity to receive ONAboNT-A injection after completing the study as standard of care for refractory NDO. We expect that ONAboNT-A will reduce urinary incontinence as well as its associated complications within our patient cohort.

16.5. Study-Related Injury

If any side effect or injury should occur, the participant should notify Dr. Smith at 713-798-4001 so that he can provide directs on how to receive appropriate medical treatment.

Research personnel will try to reduce, control, and treat any complications from this research. If a participant is injured because of this study, the participant or third party insurer is responsible for the medical care that is provided just like any other medical care.

17. WITHDRAWAL FROM THE PROTOCOL

Volunteers may discontinue participation in the study at any time without penalty or loss of benefits to which the volunteer is otherwise entitled. If possible, a volunteer who is withdrawing should complete the End of Study visit events/procedures. Volunteers participating in this study will receive \$50 for completing each of the study visits 2, 4, 5, and 6.

18. MODIFICATIONS TO THE PROTOCOL

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by BCM. Each amendment must be approved by all the principal investigators and each IRB, and if applicable, the local regulatory authority. Local requirements must be followed. If a protocol amendment requires a change to the Written Informed Consent Form, approval of the revised Written Informed Consent Form by the IRB is required before the revised form is used. The principal investigator is responsible for the distribution of these documents to his study staff and to appropriate institutional review committees.

Examples of amendments requiring such approval are:

- increases in drug dose or duration of exposure of volunteers,
- significant changes in the study design (e.g. addition or deletion of a control group),
- increases in the number of invasive procedures,
- addition or deletion of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all volunteers included in the trial. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

Changes in the staff used to monitor trials
Minor changes in the packaging or labeling of study drug
Revisions to study forms

Any deviation to the protocol that may have an effect on the safety or rights of the volunteer or the integrity of the study must be promptly reported to the IRB and other required authorities. A deviation log will be maintained by the site. The log will be tabulated into a master log and submitted with each annual IRB renewal report.

19. REPORTING UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS/ OTHERS

Reporting of unanticipated problems will be in accordance to the current IRB guidelines and FDA regulations.

An adverse event log will be maintained at the clinical site. The logs will be tabulated into a master log and submitted with each annual IRB renewal report.

20. CONTINUING REVIEW AND FINAL REPORT

Annual IRB review submissions will be made according to the local IRB's guidelines and a final report will be submitted at the completion of the study. All approvals and/or communications between the IRB and site will be forwarded to the HRPO, and any additional authorities providing oversight of this study.

21. SURVEYS, QUESTIONNAIRES, AND OTHER DATA COLLECTION INSTRUMENTS

21.1. Informed Consent Document (ICD)

Each potential volunteer will review the informed consent document with the study personnel. If the potential volunteer is willing to participate and comply with the study's requirements, the ICD will be executed.

21.2. Voiding Diary

Volunteers will complete the Voiding Diary for 7 consecutive days in the week prior to their clinic visits.

21.3. Questionnaires

Volunteers will be requested to complete the following questionnaires:

21.3.1. Incontinence Quality of Life Instrument (I-QOL) [Patrick et al, 1999]:

The I-QOL is a disease-specific, quality of life (QOL) questionnaire designed to measure QOL impact of urinary incontinence on volunteers. Designed for self-completion, the I-QOL takes approximately 5 minutes to complete. The I-QOL is scored as a total score, and 3 domain scores of Avoidance Limiting Behavior, Psychosocial Impact, and Social Embarrassment.

21.3.2. Incontinence Quality of Life Instrument Neurogenic Module [Lee et al, 2005]

The I-QOL Neurogenic Module is designed to measure the impact of urinary incontinence on volunteer's lives in a neurogenic population.

21.3.3. OAB Patient Satisfaction with Treatment Questionnaire (OAB-PSTQ)

The OAB-PSTQ is a volunteer satisfaction with treatment questionnaire created by Allergan, Inc. Volunteers' goals and expectations from treatment are assessed.

21.3.4. Patient Global Assessment (PGA)

The PGA is a global volunteer assessment that assesses the volunteer's symptoms, quality of life, activity limitations and overall emotions.

21.4. Case Report Forms (CRFs)

Protocol-specific data will be collected on Case Report Forms as required. The completed dataset is available to all the investigators, is the sole property of BCM, and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from BCM.

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APPENDIX I

SCHEDULE OF EVENTS

Schedule of Events

Events/Procedures	Consent/ Screening	Treatment and F-U Sequence				
	Visit 1 2 to 4 weeks prior to Visit 2	Visit 2 Randomization and Injection Day 1 V 1 +14 Days to 6 Weeks	Visit 3 Telephone 3-5 Days Post-Injection	Visit 4 4 wks Post-injection ± 3 days	Visit 5 12 wks Post-injection ± 3 days	Visit 6 End of Study 24 wks Post-injection ± 3 days
Consent	X					
Inclusion/exclusion	X	X				
Concomitant medications	X	X	X	X	X	X
Physical exam	X					X
Vital signs	X	X		X	X	X
Weight	X					
CBC	X					
CMP	X					X
PSA (Males Only)	X**					
Serum Pregnancy test (Females)	X	X*		X*	X*	X
Urine Pregnancy test (Females)		X		X	X	
Post void residual	X	X		X	X	X
Kidney ultrasound within 1 year	X					X
Urodynamic studies within 1 year	X				X	
Urinalysis	X	X		X	X	X
Urine C&S	X			X	X	X
Urine specimen collection for biomarker evaluation		X		X	X	X
Off meds for 2 weeks prior to injection		X				
Bladder diary	X	X		X	X	X
Assessment of total volume voided on diary		X		X	X	X
OnaBoNT-A/Placebo Injection		X				
Dispense Oxybutynin/Placebo		X		X	X	
Study product Accountability				X	X	X
Antibiotic prescription	X					
Antibiotic Accountability		X				
I-QOL		X		X	X	X
I-QOL neurogenic module		X		X	X	X
OAB-PSTQ	X			X	X	X
Patient Global Assessment				X	X	X
Adverse event assessments		X	X	X	X	X
Subject stipend for transportation		X		X	X	X

*Serum Pregnancy will be done if urine pregnancy is result is positive

PSA- **50 years or older, unless has a family history of prostate cancer or is of African American decent then PSA age to be checked is at age 40 years old

Non-standard of care is highlighted in yellow.

APPENDIX II

URINE COLLECTION PROTOCOL

**ONAbNT-A v. Oral Oxybutynin in Spinal
Cord Injured Patients with NDO
(#11-09-10-04)**

URINE COLLECTION PROTOCOL

URINE COLLECTION AND PROCESSING PROTOCOL

Samples should be processed immediately and submitted to William Beaumont Health System when a set of urine specimens from a batch of 10 patients or a reasonable size batch is complete:

1. Record the date, time of collection and the time you start sample processing on sample form.
2. Divide urine equally between two 50ml tubes of undiluted urine collected preferably from volunteers when they feel a full sensation or the need to catheterize will be used for analysis.
3. For the urine sample to be preserved (one of the 50 ml tubes):
4. Carefully cut the tip off the Norgen Urine Preservative Single Dose ampule and dispense the contents into one of the 50mL conical tubes with the urine sample. Tighten container lid. Invert several times to mix.
5. From the tube with urine+preservative, aliquot 5 mL into a pre-labeled tube.
6. Make sure both containers are securely closed and will not leak by carefully inverting. Tubes should have "P" on the label.
7. Wrap with parafilm the lids of both the 50mL tube and 5mL tube with preserved urine (this is done in case there is a leak).
8. Place in biohazard bag with absorbent material.
9. Store at room temperature out of direct light.
10. For the urine sample to be frozen (the other 50mL tube):
 - a. Spin the sample 10 min @ 650 x g at 4°C.
 - b. During the spin, add 10uL of BME to 1mL of Buffer SK and ensure all tubes to be used are labeled.
 - c. Pour off the supernatant carefully into a new 50mL tube as not to disturb or dislodge the cell pellet.
 - d. To cell pellet: Add 350 µL of Buffer SK with BME to the pellet. Lyse cells by vortexing for 15 seconds. Ensure that the entire pellet is completely dissolved before proceeding to the next step. Transfer the lysate to an RNase-free microcentrifuge tube. Add 200 µL of 100% ethanol to the lysate. Mix by vortexing for 10 seconds. Store at -80°C. Tube should have "RNA" on label.
 - e. To urine supernatant: Aliquot 1mL into ten (10) 1.5mL microcentrifuge tubes. Store at -80°C.
 - f. Discard any remaining urine.
4. Collection should immediately be placed on ice to halt enzymatic activity. Store on ice until processing. Process within 30 to 60 minutes or as soon as possible.
5. Ship OVERNIGHT with AM delivery in sufficient **DRY ICE** to:

Dr. Laura Lamb
William Beaumont Hospital Research Institute
3811 West 13 Mile Road
Royal Oak, MI 48073
(248) 551-6226

Contact several days before shipping:

Dr. Laura Lamb	laura.lamb@beaumont.org	248-551-0579
Sarah Bartolone	sarah.bartolone@beaumont.org	248-551-6226

Labeling of Tubes

- All tubes should have study ID number and date collected on them.
- For samples containing urine + preservative, after sample ID number put “-P” (e.g. 103-P). There will be one 50mL tube and one 5mL tube total.
- For sample containing urine + Buffer SK + BME + Ethanol, after sample ID put “RNA” (e.g. 103 RNA). There will be one 1.5mL tube total.
- For sample containing urine supernatant, no additional labeling is needed (e.g. 103). There will be ten 1.5mL tubes total.

URINE SAMPLE ACQUISITION FORM

(to be filled and submitted with each sample)

H #: 34972

Subject ID#: _____

Date of collection: _____

Time of collection: _____

Time samples were frozen: _____

Time started sample processing: _____

- Preservative added to 50ml sample: Yes No
- 5ml aliquot of preserved urine aliquoted: Yes No
- BME added to Buffer SK: Yes No
- Buffer SK +BME and Ethanol added to pellet: Yes No
- 10 aliquots of frozen urine made: Yes No
- Preserved samples stored at room temperature: Yes No
- Frozen Samples stored at -80 degrees C: Yes No

Time sample completed: _____

Any Additional Notes:

Name (Printed)

Signature

Date

APPENDIX III

VOIDING DIARY

**BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders
7-DAY DIARY**

Volunteer ID# _____ Visit # _____

The diary is to be completed for the 7 days in a row the week before your clinic visit. Write the current date and diary day in the **DATE** row for each day.

At the time you experience an accidental leakage of urine, rate the episode as follows in the **Leakage** column:

1 = damp or a few drops of urine

2 = wet your underwear or pad

3 = soaked underwear/clothes or emptied bladder. You may have several accidents during an hour. Please record each event.

In the **Void** column, place a check mark (√) each time you urinate in the toilet.

In the **CIC** column, please place a check each time you catheterize.

In the **Amount** column, indicate each time the number of ccs you urinated **OR** catheterized

DATE	TIME	Leakage	Void	CIC	Amount
10/1/10	12am-3:59am			√	175
	4am-4:59am				
	5am-5:59am				
	6am-6:59am			√	300
	7am-7:59am				
	8am-8:59am	1, 2			
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm	3, 1, 1			
	1pm-1:59pm				
	2pm-2:59pm			√	100
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm			√	200
	7pm-7:59pm				
	8pm-8:59pm	2			
	9pm-9:59pm			√	250
	10pm-10:59pm				
	11pm-11:59pm			√	150

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 1 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 2 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

1 = Damp or a few drops of urine on underwear;

2 = Wet your underwear or pad;

3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 3 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

1 = Damp or a few drops of urine on underwear;

2 = Wet your underwear or pad;

3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 4 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 5 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 6 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 7 of 7 DAY DIARY

Visit # _____

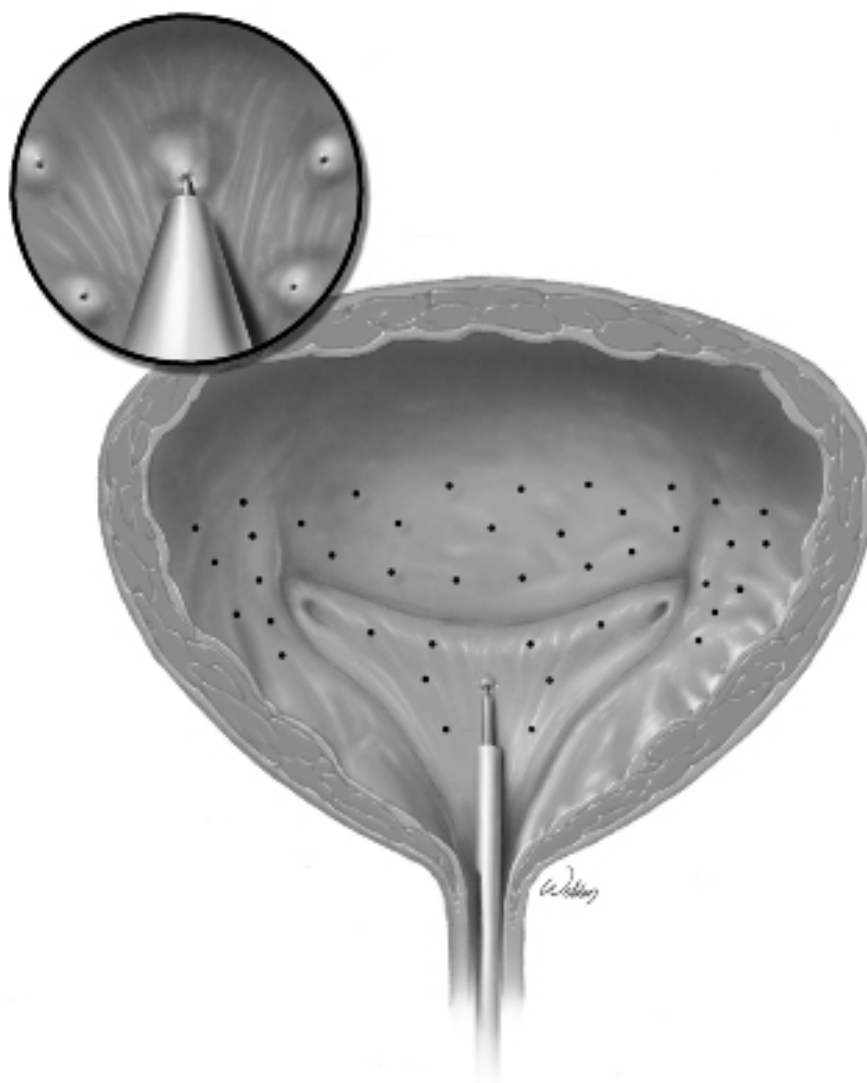
DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
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	3pm-3:59pm				
	4pm-4:59pm				
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	8pm-8:59pm				
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- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

APPENDIX IV

INJECTION DIAGRAM

INJECTION DIAGRAM



The investigator will receive 4 identically appearing syringes pre-filled with 8 mL each of reconstituted study medication (total of 32 mL) from the independent reconstitutor. The first syringe should be attached to the injection needle. 2 mL of study medication should then be used to prime the needle (resulting in a volume of 6 mL in the first dosing syringe). A total of 30 mL remains between the 4 injection syringes for study treatment administration. Each treatment session will be administered as 20 injections each of 1 mL (10u/ml), evenly distributed into the bladder. The injection needle can then be inserted into the injection port of the cystoscope for detrusor injections. Under direct visualization, injections should be distributed evenly across the detrusor walls and dome, spaced approximately 1 cm apart to include the trigone. The needle should be inserted approximately 2 mm into the detrusor for injections. The entire 30 mL will be administered as 30 injections each of 1 mL (total volume administered is 30 mL), evenly distributed into the detrusor via cystoscopy (see Injection Pattern Diagram in Appendix II). After the injections are given, the saline used for bladder wall visualization should be immediately drained. Indwelling catheters may be used during the 24-hour post-treatment period at the discretion of the investigator.

APPENDICES V

QUESTIONNAIRES

H-34972: A Multicenter, Double-Blind, Randomized Study of the Safety and Efficacy of OnabotulinumtoxinA (ONAb_oNT-A) versus Oral Oxybutynin in Spinal Cord Injured Patients with Neurogenic Detrusor Overactivity (Protocol Number 11-09-10-04)

Protocol Changes from 5/11/15 to 6/20/17

Inclusion Criteria

Section 7.1, page 16

Revised lower weight limit to 90 pounds

A Double-Blind, Randomized Study of the Safety and Efficacy of OnabotulinumtoxinA (ONAbNT-A) versus Oral Oxybutynin in Spinal Cord Injured Patients with Neurogenic Detrusor Overactivity (Protocol Number 11-09-10-04)

Protocol Version: June 20, 2017

PHASE 3B

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KEYWORDS: Botulinum Toxin, Oxybutynin, Overactive Bladder, Spinal Cord Injury, Urinary Incontinence, Nerve Growth Factor, Urine Biomarkers

BCM IRB NUMBER: H-34972 (TIRR Memorial Hermann)

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1. BACKGROUND

1.1 Pathophysiology of Neurogenic Bladder (NGB) due to Spinal Cord Injury (SCI)

Overactive bladder is a condition resulting from disruption of the normal micturition process. It is a syndrome complex characterized by urinary urgency and frequency that may or may not be accompanied by incontinence. Incontinence is due to involuntary contraction of the bladder smooth muscle during bladder filling (detrusor overactivity). [Mills et al, 2000] Neurological disease involving the spinal cord can result in incontinence secondary to a loss of inhibitory input from the micturition center and from interruption of the spinobulbospinal pathways which normally control bladder behavior. The result, demonstrable on urodynamic evaluation, is abnormal involuntary detrusor contractions, often leading to incontinence. In addition, such patients frequently also suffer from urethral sphincters that are unable to relax prior to micturition in a coordinated fashion (i.e. detrusor-sphincter dyssynergia). This lack of coordinated activity can result not only in incontinence but also in vesico-ureteric reflux and/or high storage and voiding pressures which, if left untreated, can lead to potential renal damage. [Foley et al, 1997]

1.2. Epidemiology and Burden of SCI induced NGB

Approximately 10,000 SCIs occur each year, most of which occur in males (80%) [De Vivo et al, 1992]. Many of these patients develop neurogenic bladder dysfunction (NGB) characterized by overactivity of the detrusor muscle, termed neurogenic detrusor overactivity (NDO) or the older term detrusor hyperreflexia (DH). Spinal cord injured patients can also develop detrusor external sphincter dyssynergia (DESD), an abnormal/uncoordinated response of the sphincter to bladder contraction. A combination of these factors can lead to *long-term complications in up to 50% of patients* [Kaplan et al, 1991; McGuire 1979; Yalla et al, 1977]. These complications include hydronephrosis, autonomic dysreflexia, vesicoureteral reflux, nephrolithiasis, sepsis, renal insufficiency or failure and even death. SCI patients often suffer from urinary incontinence which can lead to adverse events such as urinary tract infections and decubitus ulcers, in addition to creating a large care burden for family members or healthcare providers and significantly impairing the veteran's quality of life. Clearly, bladder problems related to SCI have a negative impact not only on patients' physical condition, but also on their emotional and social well-being. Low self-esteem resulting from urinary incontinence can reduce social interaction, depress sexual desire, and interfere with productivity at work, in school, or during rehabilitation of the veteran's primary neurological disease.

1.3. Current Treatment of NGB is Inadequate

Common pharmacologic treatments to reduce bladder contractility include anticholinergics, antispasmodics and tricyclic antidepressants. However, these therapies have limited efficacy and are associated with a high incidence of side effects including dry mouth, constipation and blurred vision [Ouslander, 2004]. A large randomized trial comparing propiverine to oxybutynin in SCI patients found that oxybutynin only reduced daily incontinence episodes by 39%. [Stohrer et al, 2007]. Furthermore, anticholinergic adverse effects were observed in 78% of oxybutynin treated patients in parallel with the limited benefit of the drug in reducing bladder related incontinence. In fact, a large epidemiological study of oral antimuscarinic drug use among NGB patients found that 38% stop therapy within one year of initiation of therapy. [Manack et al, 2011]

Although a large proportion of NGB patients are inadequately treated with standard front-line therapy with oral anticholinergics, up until recently, the only options available to patients who do not respond to or discontinue anticholinergic therapy are invasive procedures such as implantable devices to chronically stimulate the sacral nerve (i.e. limited studies showing utility in NGB patients) or surgical bladder augmentation (i.e. where intestine is harvested and sewn onto the bladder). While these procedures may be effective for some patients, they are highly invasive, expensive, do not necessarily guarantee continence, and may have long term complications [Bosch and Groen, 1998; Bosch, 1998].

1.4. OnabotulinumtoxinA (ONAbNT-A) as an Alternative Treatment of Refractory NGB

Botulinum toxin is a neurotoxin that acts by inhibiting neurotransmitter release from nerve endings. It is commonly used to treat conditions of skeletal muscle spasticity (i.e. cervical dystonia, etc.). In contrast to muscarinic antagonists whose primary beneficial effects are mediated by inhibiting parasympathetic mediated cholinergic transmission to the bladder, ONAbNT-A's denervating effects are widespread. In fact, ONAbNT-A has been shown to inhibit the release of multiple neurotransmitters (i.e. acetylcholine, ATP, norepinephrine) and growth factors (i.e. nerve growth factor, NGF) that depend on SNARE (i.e. soluble N-ethylmaleimide-sensitive factor attachment protein (SNAP) receptor) mediated release from nerve endings. [Abdel-Meguid, 2010] The use of ONAbNT-A in the urinary bladder was first described by Schurch and colleagues who demonstrated a significant increase in mean maximum bladder capacity (296ml to 480ml, $p < 0.016$) and a significant decrease in mean maximum detrusor voiding pressure (65 to 35cm H₂O, $p < 0.016$) in 21 patients with NDO that were injected with ONAbNT-A. [Schurch et al, 2000] A strong impetus driving industry sponsored clinical trials examining the effects of ONAbNT-A on NDO was provided by the first randomized, placebo-controlled trial examining the effects of two doses of ONAbNT-A (i.e. 200 or 300 units) versus saline injection on various parameters including urodynamic measurements and urinary incontinence episodes in patients with refractory NGB resulting from multiple sclerosis (i.e. MS) or SCI. [Schurch et al, 2005] Significant decreases in incontinent episodes (i.e. approximately 50%), significant increases in maximal cystometric capacity (i.e. approximately 170-215ml), and significant improvements in quality of life scores were demonstrated in both ONAbNT-A treatment groups compared to controls. Beneficial effects lasted the duration of the study (i.e. 6 months).

A second double-blind, randomized, placebo controlled study compared the effects of ONAbNT-A (300 U) in 57 patients with urinary incontinence resulting from MS or SCI. At 6 weeks following treatment, ONAbNT-A treated patients demonstrated a 57% reduction in daily incontinence episodes compared to no change in placebo treated patients. [Herschorn et al, 2011] Most recently, a Phase 3 double-blind, placebo-controlled, parallel group study compared the effect of two doses of ONAbNT-A (i.e. 200 U and 300 U) to placebo in 416 patients with urinary incontinence and NDO resulting from multiple sclerosis or SCI and not adequately managed with antimuscarinic medication. At 6 week follow-up, 200 U of ONAbNT-A reduced weekly urinary incontinence episodes by 69%, a significantly greater response than placebo treatment (i.e. 29%). [Ginsberg et al, 2011]

The preceding three randomized studies demonstrate that ONAbNT-A is more effective than placebo for improving the symptoms and signs of NDO, as measured by the reduction in episodes of urinary incontinence as well as improvements in urodynamic parameters. However, in each study **patients were allowed to remain on anticholinergic treatment throughout the duration of the study** so the absolute benefit of ONAbNT-A treatment cannot be assessed.

Moreover, although patients in each study were determined to be refractory to antimuscarinic treatment, the relative effectiveness of antimuscarinic medication versus ONAboNT-A in patients SCI patients suffering from urinary incontinence can only be determined through a randomized, controlled, trial comparing single treatment with either agent.

Finally, prior randomized trials have all excluded bladder trigone injections for fear of inducing vesicoureteral reflux. Studies have disproven this theory and, in fact, mounting evidence suggests that the bladder trigone is an ideal target for ONAboNT-A injections. [Smith et al, 2005; Abdel-Meguid, 2010] For starters, the bladder trigone is densely innervated and contains an abundant concentration of the high-affinity binding site for ONAboNT-A, SV2. [Coelho et al, 2010] Moreover, a recent randomized comparative trial between trigone and non-trigone bladder injection paradigms in patients with SCI induced NDO found that including trigone injections led to significantly greater improvements in urinary incontinence. [Abdel-Meguid, 2010] These findings parallel Dr. Smith and Dr. Chancellor's 14 year personal experience utilizing bladder trigone injections with ONAboNT-A. [Smith et al, 2005]

1.4.1 Use of ONAboNT-A to Treat SCI NGB Patients

We recently reviewed our results using ONAboNT-A in a high-risk population of SCI patients with NGB and decreased bladder compliance. Loss of detrusor compliance creates high urine storage pressure in the bladder with consequent risks to renal function. Data were collected from 24 patients with urinary incontinence secondary to SCI, all of whom underwent intradetrusor injection of ONAboNT-A at The Institute for Rehabilitation and Research (TIRR). [Mengheang et al, 2011] Each patient underwent injection of 300 units of ONAboNT-A, with the exception of one patient who received 100 units.

A total of 24 patients with incontinence of neurogenic origin were included in this study. Mean patient age was 33 years (range 15 to 65), and mean time since SCI was 8.5 years (range 7 months to 24 years). Of the 24 patients, 11 had cervical SCI, 8 had thoracic SCI and 2 had lumbar SCI; the other three patients suffered from transverse myelitis, spinal cord malacia, and cerebral palsy.

Overall, there was significant improvement in urodynamic parameters after ONAboNT-A injection (Table 1).

	Baseline	Follow-up	P value
Compliance (ml/cm H ₂ O)	14 ± 2	29 ± 5	0.002
Maximum cystometric capacity (mL)	322 ± 32	421 ± 33	0.008
Maximum det/ves pressure (cm H ₂ O)	59 ± 4	36 ± 5	<0.001
Reflex detrusor volume (mL)	155 ± 22	187 ± 33	0.37

Table 1. Urodynamic parameters at baseline and follow-up after ONAboNT-A injection

Notably, 22 (92%) of the 24 patients had low baseline compliance, defined as <20 ml/cm H₂O (mean 14 ± 2ml/cm H₂O). In this subset of 22 patients, baseline compliance increased 260% post-treatment, from a mean of 11.2 ± 1 to 29.2 ± 5 ml/cm H₂O, p=0.001 (Figure 2). Seventeen patients (77%) with low baseline compliance had an increase in compliance on follow-up urodynamics.

Furthermore, 18 of the 24 patients had an elevated maximum detrusor pressure (MDP) > 40 cm H₂O with reduction of MDP into the normal range in 9/18 (50%) after ONAboNT-A therapy. Overall, the mean MDP decreased from 59 ± 4 to 36 ± 5 cm H₂O.

Figure 2: A subset of 22 patients with incontinence of neurogenic origin responded to intradetrusor injection of ONAboNT-A with a 260% post-treatment increase of baseline compliance from 11.2 ± 1 to 29.2 ± 5 ml/cm H₂O, p=0.001

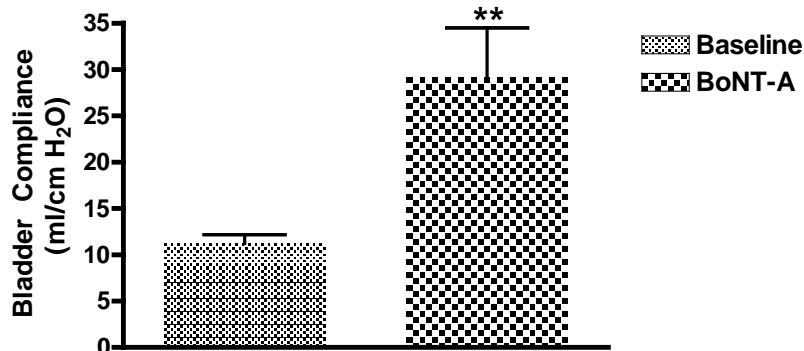


Figure 2. Bladder Compliance

Detrusor overactivity was documented in twenty-three of the 24 patients (96%) during urodynamic study (i.e. documented occurrence of an uninhibited contraction during bladder filling). Post-injection, only 11 (46%) of the 24 patients had uninhibited contractions on urodynamics. There was an increase in reflex detrusor volume on follow-up urodynamics, but it was not statistically significant.

Favorable clinical response was defined as a decrease in frequency of catheterization and/or absence of incontinence episodes. Eighteen of 24 patients (75%) reported a favorable clinical response as defined above. Of the 12 patients with low baseline compliance that experienced improvement in the normal range, 11 (92%) had a favorable clinical response.

1.4.2 Results

In summary, ONAboNT-A bladder injection can significantly improve objective and subjective parameters in SCI patients with high-risk bladders (i.e. decreased bladder compliance). In addition to prior clinical publications between Drs. Smith and Chancellor, [Smith et al, 2005] this data establishes these investigators as clinical experts in the application of ONAboNT-A to patients with urinary incontinence and NGB.

1.5. Urinary Biomarkers in Bladder Dysfunction

Existing therapeutic outcome measures for NGB patients heavily rely on subjective impressions of patients leading to high heterogeneity in clinical response to neuromodulation achieved either by pharmacological or physical means. In the studies described for Aim 2, we will test the following hypothesis to substitute a response variable continuous in nature (i.e. urinary biomarkers) in addition to subjective clinical outcome (i.e. change in urinary incontinence episodes). Nerve growth factor (NGF) is a potent neuronal growth factor with nociceptive and inflammatory properties recently shown to be of importance in bladder pathology. NGF is a

target organ derived growth factor that is produced by most organs lining the upper and lower urinary tract following pathologic insult. [Yoshimura, et al, 2006] NGF is known for neuroimmune interactions. NGF and its receptors may also amplify other immunoinflammatory and neuronal pathways contributing to bladder inflammation and leading to symptoms associated with NGB. We have previously demonstrated that urine NGF levels are elevated in various conditions of bladder dysfunction (i.e. interstitial cystitis, NDO) and can be reduced following bladder injection with ONAboNT-A. [Liu et al, 2009a; Liu et al, 2009b] Taken together, our preliminary data indicate that activation of the NGF and a network of chemokines represents a pivotal final pathway that can be used to construct a biomarker panel for analyzing NGB patients and assessing their treatment response to ONAboNT-A or oxybutynin.

Our hypothesis is that immune and neuronal mechanisms integrate to produce neuroimmune responses as an adaptive mechanism responding to SCI. A dense network of sensory nerve fibers is strategically placed just below the bladder epithelial surface so that any change in the urothelial environment may stimulate the release of proinflammatory neuropeptides by chemokines. [Gabella, 1999; Qin et al, 2005] Chemokines are chemotactic cytokines that constitute a large family of secretory proteins with a molecular weight of 7-10 Kd that are expressed by leukocytes and resident tissue cells.[Mortier et al, 2008] Chemokines exert their effect by interacting with G protein-coupled receptors present on glycosaminoglycans that are linked to endothelial cell layers. [Mortier et al, 2008] Recent studies have shown that chemokines may represent a group of neuromodulatory agents that can alter sensory processing in bladder. [Torrence et al, 2007; Yuridullah et al, 2006] Statistics favor that a panel of independent urinary markers composed of NGF and chemokines will be better than sole reliance on a single urine marker as a surrogate of efficacy of ONAboNT-A and oxybutynin treatment.

Studies have shown that cytokines/chemokines and chemokine receptors are not uniquely restricted to inflammation, but are also responsible for autocrine, paracrine and endocrine signaling by non-immune cells in the bladder such as urothelium and detrusor muscle cells. [Bouchelouche et al, 2004; Bouchelouche et al, 2006] Apart from infiltrated mononuclear cells, recent studies demonstrate that bladder inflammation can be amplified by the resident cells themselves in urothelium through the release of chemoattractants for various inflammatory cells. [Billips et al, 2007; Apostolidis et al, 2008; Schwentner et al, 2008] Previous pre-clinical studies in our lab have already shown that inflammatory signaling is reflected by levels of cytokines in biological fluids interacting with inflamed tissue [Tyagi et al, 2009b]. One of the crucial host defense responses is neutrophil migration to injured urothelium that involves a series of complex interactions with molecules in the lamina propria and at the epithelial barrier. [Godaly et al, 2001] The proteins measured in the urine of NGB like chemokine monocyte chemoattractant protein (MCP-1) and NGF have an established biological role in sensitizing afferents and producing symptoms associated with NDO. [Bhangoo et al, 2007] MCP-1 has also been shown to increase afferent excitability by sensitization of TRPV1 receptor on afferents and the mechanosensitive variant TRPA1 receptors [Jung et al, 2008]. The elevated urinary MCP-1 levels in patients with NGB may be responsible for exacerbation of symptoms by increasing afferent nerve excitability through modulation of TRPV1. The relationship of elevated MCP-1 with symptoms can also be explained by the dose dependent inhibition of GABAergic neurons by MCP-1. [Gosselin et al, 2005; Melik-Parsadaniantz and Rostene, 2008] GABAergic transmission is inherently inhibitory in nature and is likely to attenuate nociceptive transmission. [Miyazato et al 2008]

Urinary proteomics is an attractive option for clinical use, as urine is an ideal source for the discovery of noninvasive biomarkers for human diseases. Therefore, urine presents a rich

source of information for bladder diseases. Disease induced changes in urinary proteome can be traced to overexpression of proteins or abnormal shedding from urothelium into urine. [Tyagi et al, 2009a] Chemokines are subdivided into 4 families (CXC, CC, C and CX₃C) based on the relative position and number of conserved N-terminal cysteine residues as well as the absence (CC) or presence of intervening amino acid(s) between the cysteine residues (CXC). The CC and CXC family have more than one of its members that are implicated in inflammatory pathways.

Many studies have examined the urine as a possible source for biomarkers of urogenital disease because urine is in direct contact with the bladder and prostate and the molecular composition of urine can reflect biochemical and pathophysiological changes in the those organs. [Erickson et al, 2002]

Most of the biomarkers currently used in the clinic have emerged from targeted analysis of candidate biomarkers using immunoassays. [Pirtskalaishvili et al, 1999; Kronborg et al, 2007]] By focusing on a limited number of candidate biomarker proteins, assay technologies providing higher sensitivity and dynamic range such as Luminex can be used. Multiplexed immunoassays (i.e. Luminex) have allowed the measurement of biomarkers associated with bladder dysfunction with very low concentrations in urine that could not be measured for full patient cohorts with conventional immunoassays. In the proposed study, urine levels of chemokines and growth factors will be measured by multiplexed immunoassay panel and normalized by urinary creatinine levels.

The best-established microsphere assay system is the Luminex xMap system (Luminex Corp., Austin, TX), incorporating proven time tested technologies: bioassays, solution phase microspheres, and flow cytometry. [Tyagi et al, 2009a] The antibody specificity of multiplex immunoassays offers simultaneous analysis of a set of markers that can form a fingerprint of the patient responding to treatment with improved sensitivity and specificity. Sensitivity and specificity of biomarkers have been found to be potentiated by use of immunoassay panels which include chemokines, cytokines and angiogenic factors. The sandwich format utilized in the bead based assay as in traditional ELISA not only provides higher-specificity but also minimizes cross-reactivity with other urinary proteins.

1.5.1 Utility of Urinary Biomarkers in Bladder Dysfunction

Studies have shown that cytokines and chemokines responsible for autocrine, paracrine and endocrine signaling are also released by non-immune cells in the bladder such as urothelium and detrusor cells. [Bouchelouche et al, 2004; Bouchelouche et al, 2006a; Bouchelouche et al, 2006b] The urinary bladder relies on a broad array of cytokines, chemokines and growth factors to effect biochemical changes within its organ in response to disease and therapeutic intervention. But not all these chemokines/cytokines and growth factors can serve as urinary biomarkers or surrogates of treatment response as they have to fulfill the key requirement of being present in detectable amounts in urine that can be assayed using standard methods.

For example, although tumor necrosis factor (i.e. TNF) - α is the initiator of the inflammation process in the bladder, it is unlikely to serve as a urine marker for bladder inflammation [Billips et al, 2007; Bouchelouche et al, 2006a], because of its very small amount released into the urine. [Sadeghi et al, 2005] It is quite possible that released TNF- α binds with receptors in surrounding tissue such that only trace amounts are leaked into the urine. Thus, the release of cytokines and other inflammatory mediators into the urine is critical for their utility to serve as a biomarker. With the availability of reliable analysis methods based on immunoassays such as

ELISA, numerous studies have used cytokines as biomarkers in the diagnosis and prognosis for a host of diseases. [Parekattil et al, 2003; Parikh et al, 2006; Rovin et al, 2005; Segerer and Nelson, 2005; Mehta, 2006]

In contrast to urine levels of TNF- α in NGB patients, the detectable amount of NGF in the same patients combined with its known role in neuroimmune interactions makes NGF an ideal candidate for a urinary biomarker. A role for NGF in the development of UTI is not well elucidated and the aims of our preliminary study were to investigate the secreted levels of NGF in urine from symptomatic UTI patients in comparison to patients with asymptomatic bacteriuria (ASB) in SCI patients. Our hypothesis is that immune and neuronal mechanisms integrate to produce neuroimmune responses to ward off UTI, but not ASB. Therefore, changes in urinary NGF levels will reflect the status of the host immune response in lower urinary tract, whether related to ASB or UTI. NGF and its receptors may also amplify other immunoinflammatory and neuronal pathways contributing to bladder inflammation and symptoms associated with UTI.

1.5.2 Elevated Urine NGF Levels in Spinal Cord Injured Patients with Urinary Tract Infection (UTI) but not Asymptomatic Bacteriuria (iASB)

Table 2. Urinary NGF levels in 18 SCI patients.

Time	Urine samples	Urinary total NGF (pg/ml)	Urinary NGF/Cr	Statistics
Baseline ASB	18	4.6 \pm 1.5	0.1 \pm 0.1	
Week 1				
1. ASB and non UTI	13	8.3 \pm 2.1	0.2 \pm 0.1	$p=0.01^*$
2. Symptomatic UTI	5	77.8 \pm 17.3	1.1 \pm 0.5	$p=0.79^\#$
Week 2				
1. ASB and non UTI	9	5.1 \pm 1.8	0.1 \pm 0.1	$p<0.01^*$
2. Prev. symptomatic UTI treated with ABX and now asymptomatic	5	12.8 \pm 8.8	0.2 \pm 0.2	$p=0.04^{**}$
3. New onset Symptomatic UTI	4	85.6 \pm 42.2	1.3 \pm 1.0	$P= 0.75^{**}$

* comparison of urinary NGF/Cr level between the control and disease condition,

comparison of NGF/Cr level between baseline and time point, ** comparison between treated and post-treatment

A pilot study of 18 SCI men at an inpatient spinal cord injury center was carried out. The patients enrolled in the study were at their initial hospitalization after suffering from SCI due to: motor vehicle accidents 11, fall 4, diving 2, and work accident 1. Ten patients were paraplegic and 8 were quadriplegic with a mean age of 38.4 \pm 19 years old. All patients had indwelling catheters during their initial spinal shock phase and all patients demonstrated a positive urine culture (i.e. $>10^5$ colonies/cc). Twelve cultures grew out E. Coli, two cultures grew Staphylococcus aureus, three cultures grew Pseudomonas aeruginosa, and one culture was positive for Klebsiella. None of the men had a history of recurrent UTI's, incontinence, lower urinary tract symptoms, or renal dysfunction prior to SCI, except for one patient that had a renal calculus which passed spontaneously 4 years earlier and another patient that was a Type-2 diabetic.

Sample Purification: Urine was collected from the catheter by nurses from consented patients and an aliquot of urine specimens was sent immediately for urine culture. The remainder of the collected urine samples was immediately placed on ice to prevent degradation by endogenous proteases. Urine was centrifuged for 5 min at 10000 x g to remove cell particles and supernatants were passed through 0.34 mm Whatman chromatography paper. Filtrates were divided into aliquots and transported immediately to the -80°C freezer or maintained at 4°C until transported to the freezer within 4 hours. After removal of cell debris and nuclei, the supernatants underwent microscopic examination with a hemacytometry counting chamber to verify absence of cells or particles.

Using traditional ELISA technique, we investigated the levels of NGF in the urine of ASB and UTI patients. The samples were assayed in triplicate by antigen capture ELISA (Promega, Madison, WI) according to the manufacturer's instructions. The results as shown in Table 2 noted a significant five fold elevation of normalized NGF in UTI versus ASB patients. This was confirmed on two separate group of patients at one and two weeks post catheterization with development of UTI symptoms including new onset of urine leakage around catheter (n=4), new onset bladder spasm (n=4), fever (n=2), and increase in WBC count to above normal range (n=3). A greater than 5 fold elevation of NGF in the urine of UTI patients relative to ASB indicates that NGF is an important mediator of host response towards infection. Moreover, oral antibiotic treatment of five patients with symptomatic UTI for one week significantly decreased the elevated urine NGF relative to values obtained before antibiotic treatment. These results suggest that neuronal mechanisms are important in UTI and subsequent symptoms of urinary frequency. Urinary tract induced release of NGF is likely to lead to short and long term changes in the distribution and reactivity of sensory nerves across the lower urinary tract, promoting exaggerated inflammatory reactions during and after the infection.

On the basis of these observations, we postulate that changes of neurotrophin expression such as NGF in the lower urinary tract may represent an opportunity to separate ASB from UTI. In summary, a biomarker panel developed using a combination of NGF and selected chemokines can be a useful measure in differential diagnosis of UTI versus ASB. It can also be useful as a prognostic indicator of bacteriuria invasion of bladder wall with development of bladder inflammation response that may help judicious use of antibiotic therapy and curb the menace of bacterial resistance.

1.5.3 Urine Chemokine and Growth Factor Levels in Neurogenic Bladder Patients

In a different set of 13 patients with NGB collected from a different clinical site, with a history of SCI or other neurological diseases like MS or diabetes, we analyzed urinary chemokines and growth factors in addition to NGF in a single time point urine specimen, processed similar to NGF analysis above. We were able to consistently detect the following proteins in the urine of these patients: interleukin IL-5, IL-6, IL-1Ra, sIL-2R α , CC chemokines including MCP-1, MIP-1 β , RANTES(Regulated upon Activation, Normal T Expressed and Secreted), CXC chemokines including GRO- α / CXCL1, IL-8, and IP-10 and growth factors including vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet derived growth factor (PDGF-AA), VEGF, PDGF, and NGF (Figure 3). [Jacobs et al 2010]. The detected proteins were part of a screen composed of 32 proteins. Levels of urinary proteins were normalized to the concentration of creatinine (Cr). We will target these proteins to evaluate the effect that ONAbNT-A or oxybutynin ER has on their expression in urine. The selected proteins can be categorized as:

Afferent sensitizers: NGF, MCP-1, IP-10

Pro-inflammatory chemokines/ cytokines: IL-5, IL-6, GRO-a, IL-8, RANTES, MIP-1b,

Angiogenesis mediators: VEGF, PDGF

Ant-inflammatory Proteins: IL-1RA, sIL-2Ra

1.5.4 Changes in Urine Biomarker Levels with Treatment

To demonstrate our ability to detect treatment related changes in urinary proteins, we present data gathered from our pilot study in patients with another model of bladder dysfunction (i.e. interstitial cystitis/painful bladder syndrome (IC/PBS)) implanted with the InterStim® neuromodulator. In contrast to neuromodulation achieved by pharmacological method (ONAbNT-A), the neuromodulation of IC/PBS patients was achieved by physical means using electrical stimulation of afferent nerve fibers by calibrated frequencies of an implanted neurostimulator device (i.e. InterStim®). IC/PBS patients recruited for the study had symptoms of urinary urgency and frequency and bladder pain for at least 3 of the 6 months immediately before the first visit. Enrolled patients had O'Leary-Sant Interstitial Cystitis Symptom Index (i.e. ICSI) and Interstitial Cystitis Problem Index (i.e. ICPI) scores of 20 or higher and patients with pelvic mass, pelvic prolapse, urinary retention, and pelvic malignancies as revealed by physical examination were excluded. Clean catch midstream urine specimens was obtained from patients at baseline (prior to implant of interstim) and at 4, 12, and 24 weeks after implant. Enrolled patients also provided ICSI and ICPI scores at each time a urine specimen was collected. Urine samples were collected in 50ml conical tubes and then centrifuged for 10 minutes at 5,000 x g to remove cells as sediment. Supernatant was removed and divided into 1.5 ml aliquots (cryotubes) and transported immediately to the -80°C freezer or maintained at 4°C until transported to a -80°C freezer within 4 hours. The technique used to measure urinary proteins is illustrated in figure 4.

The decline in urinary chemokines of IC/PBS patients with InterStim treatment correlated with decreased ICSI scores suggesting that symptomatic improvements in a patient's condition measured by the subjective scale of ICSI score was associated with objective measures of temporal changes in urinary levels of chemokines and growth factors. It was clearly apparent that IC/PBS disease is heterogeneous in nature and the patients' respond differently to the same degree of neuromodulation. Variable patient response to electrical as well as to chemical neuromodulation (i.e. injection of botulinum neurotoxin) emphasizes the need for personalized objective monitoring of patients subjected to these treatments using biomarkers.

In summary, use of a multiplexed immunoassay panel (Luminex xMap system) demonstrates its utility in serving the stated objectives of this proposal. The antibody specificity of multiplex immunoassay offers simultaneous analysis of a set of markers that can form a fingerprint of a patient responding to treatment with improved sensitivity and specificity. Multiplexed immunoassays (Luminex) have allowed the measurement of biomarkers associated with bladder dysfunction with very low concentrations in urine that could not be measured for full patient cohorts with conventional immunoassays. These techniques also allow simultaneous evaluation of multiple biomarkers in microlitre volumes of urine sample.

2. STUDY DRUGS

2.1. ONAbNT-A (onabotulinumtoxin A, Botox®, Allergan Inc., Irvine, CA)

ONAbNT-A will be the active formulation. Each vial of ONAbNT-A Purified Neurotoxin Complex, Formulation No. 9060X, contains: 100 units (U) of *Clostridium botulinum* toxin type A,

0.5 mg albumin (human), and 0.9 mg sodium chloride in a sterile, vacuum-dried form without a preservative. One U corresponds to the calculated median lethal intraperitoneal dose (LD50) in mice. A 0.9% sterile saline (without preservative) for injection will be used as diluent for ONAboNT-A.

The ONAboNT-A treatment will be administered once as 20 injections each of 1 mL (10U/ml), evenly distributed into the bladder.

Side Effects: ONAboNT-A: It is expected that some participants may have some or all of the following side effects when given ONAboNT-A. Other side effects may occur which were not seen before. Side effects are usually temporary and manageable. However, it is possible they could cause serious disease or death. The study may include risks that are unknown at this time.

Based on the results of the experimental testing in animals, there may have an increased risk of development of bladder stones.

There have been rare reports of serious and/or immediate or even deadly abnormally sensitive reactions after treatment with ONAboNT-A. These reactions include allergic reaction, skin rash, itching, swelling, and difficulty in breathing.

It is a rare possibility that the injection of ONAboNT-A could lead to botulism. The classic symptoms of botulism include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. The doctor's examination may reveal that the gag reflex and the deep tendon reflexes like the knee jerk are decreased or absent.

There have been rare reports of sudden death, sometimes associated with difficulty in swallowing or pneumonia. There have also been rare reports of heart problems (including irregular heartbeats and heart attack, some resulting in death). Some of these patients were already at risk for heart disease. It is not known if ONAboNT-A actually caused these problems.

It should not be used when infection is present at the injection site or in people known to be abnormally sensitive to ONAboNT-A.

The following events have been observed since it has been marketed: skin rash, itching, and allergic reaction. In general, these side effects occur within the first week following injection and, while usually temporary, they may last several months. Pain, tenderness, or bruising around the injection site may also occur. Local weakness of the injected muscle(s) is expected. Weakness of nearby muscles may also occur due to spread of ONAboNT-A.

ONAboNT-A contains albumin, which comes from human blood. Although the blood is rigorously tested, there is an extremely remote risk for the transmission of viruses and similar infectious agents.

ONAboNT-A placebo (saline) will be the control formulation.

2.2. Oxybutynin Chloride ER (Ditropan XL[®], Teva Pharmaceuticals USA, Sellersville, PA)

Oxybutynin Chloride ER in a 10 mg capsule will be taken twice daily for the course of the study.

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (anti-nicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that Oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Common Side Effects: Blurred vision; constipation; diarrhea; dizziness; drowsiness; dry eyes, nose, skin, or mouth; headache; indigestion; nausea; runny nose; stomach pain or upset; trouble sleeping; weakness.

Severe Side Effects: Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); confusion; difficult or painful urination; fast or irregular heartbeat; fever; hallucinations; mental or mood changes (e.g., agitation); seizures; swelling of the hands, ankles, or feet; vision problems.

Oxybutynin chloride is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin chloride is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

The concomitant use of Oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

The safety of Oxybutynin chloride administered to women who are or who may become pregnant or are breastfeeding has not been established. Therefore, Oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Placebo oxybutynin will be compounded to match the oxybutynin.

The study drugs, ONAboNT-A, ONAboNT-A placebo, Oxybutynin, Oxybutynin placebo will be prepared for randomization by investigational pharmacy. The pharmacy will maintain the drug accountability, perform the randomization, and provide the study drugs to the PI. At the completion of the study, the pharmacy will dispose of unused drug per their standard operating procedures.

3. PURPOSE

This purpose of this clinical research study is to evaluate the safety and efficacy of 200 U ONAboNT-A injected into the detrusor versus oral oxybutynin for the treatment of urinary incontinence (UI) caused by neurogenic detrusor overactivity (NDO) in spinal cord injured volunteers. At baseline and each follow-up period, urine will be collected for analysis of biomarkers for nerve growth factor (NGF) and chemokines/cytokines to determine the potential role of urine biomarkers as patient selection and surrogate endpoints of treatment outcome predictors.

4. STUDY DESIGN

This will be a Phase 3B, double-blind, randomized, placebo-controlled, parallel-group study to assess the safety and efficacy of ONAboNT-A or 10 mg twice a day of oral oxybutynin hydrochloride ER in spinal cord injured volunteers diagnosed with neurogenic detrusor overactivity.

5. STUDY POPULATION

A total of 36 volunteers will be recruited for this study. Volunteers will include both males and females with spinal cord injuries who are 18 to 80 years of age and diagnosed with neurogenic detrusor overactivity. The volunteers will be patients at TIRR Memorial Hermann in Houston, TX. There are no eligibility restrictions as to race or ethnicity.

6. RANDOMIZATION

Volunteers will be randomized using a blocked randomization approach designed by the statistician and implemented by the investigational pharmacy: ARM 1: ONAboNT-A 200 U bladder injection and placebo oral capsule daily or ARM 2: Placebo bladder injection (saline) and oxybutynin ER 10mg capsule twice daily. Subjects will be randomized into one of the two treatment arms, using a block size of 4. The order in which the treatments are assigned in each block is randomized and this process is repeated for consecutive blocks of subjects until all subjects are randomized. This process ensures that after every fourth randomized subject, the number of subjects in each treatment group is equal. Volunteers will be encouraged to washout of medication for 14 days. If they choose to remain on medicine, they will stay on same dose for duration of the study

7. ELIGIBILITY CRITERIA:

7.1. Inclusion

To be included in the study, volunteer must meet the following criteria at screening and Randomization/Day 1:

1. Volunteer is male or female, aged 15 to 80 years old.
2. Volunteer weighs at least 90 lb or more.
3. Written informed consent has been obtained.
4. Written Authorization for Use and Release of Health and Research Study Information has been obtained.

5. Volunteer has urinary incontinence as a result of neurogenic detrusor overactivity for a period of at least 3 months prior to screening as a result of spinal cord injury determined by documented patient history.
6. Spinal cord injury volunteers must have a stable neurological injury occurring at least 6 months or more prior to screening.
7. Volunteer has detrusor overactivity (defined as a phasic rise in bladder pressure during the filling phase determined by urodynamics) demonstrated during the screening period or within 1 year of screening.
8. Volunteer is able to complete study requirements including bladder diary completion and attend all study visits (telephone and clinic), in the opinion of the investigator.
9. Volunteer has a negative pregnancy result if female and of childbearing potential.

The following criteria are also required for entry into the study at Randomization/Day 1:

10. Volunteer experiences at least 14 episodes or more of urinary incontinence per week, including urinary incontinence between scheduled intermittent catheterization, with no more than 2 incontinent-free days, determined by completion of bladder diary during the screening period.
11. Volunteer currently uses or is willing to use clean intermittent catheterization (CIC) to empty the bladder (indwelling catheter is not permitted). Volunteers currently on CIC should be willing to maintain an established CIC frequency throughout the study. Caregiver may perform CIC.
12. Volunteers with a negative urine culture result must take an antibiotic medication for 3 days immediately prior to Randomization/Day 1, on Randomization/Day 1, and agree to continue antibiotic medication for at least 3 days following treatment. Volunteers with a positive urine culture result indicating urinary tract infection (UTI), must take an antibiotic to which the identified organism is sensitive for at least 3 days immediately prior to Randomization/Day 1, on Randomization/Day 1, and continue for 3 days following the procedure (or longer as needed). Antibiotics should be taken for at least 7 days. A UTI is defined as either a positive urine culture result with a bacteriuria count of more than 10^5 CFU/mL conjoint with a leukocyturia more than 5/hpf at screening with urinary tract symptoms or a positive urine culture that, in the investigator's opinion, requires antibiotic therapy.

7.2. Exclusion

Volunteers will be excluded from the study for any of the following criteria at screening or Randomization/Day 1:

1. Volunteer has history or evidence of any pelvic or urological abnormalities including but not limited to the following:
 - elevated serum creatinine more than 2 times the upper limit of normal (reference range)
 - current or history of hematuria, 1) if the hematuria is determined to be a pathologic condition or 2) is uninvestigated
 - interstitial cystitis in the opinion of the investigator

- bladder stones within 6 months of screening
 - surgery or bladder disease other than detrusor overactivity that may impact bladder function with the exception of surgeries for bladder stones (more than 6 months) and stress incontinence, uterine prolapse, rectocele, or cystocele (more than 1 year) from screening.
2. Volunteer has had previous or current botulinum toxin therapy of any serotype for any urological condition within 9 months.
 3. Volunteer has a significant stress component to their urinary incontinence (i.e. stress urinary incontinence) in the opinion of the principal investigator.
 4. Volunteer has a history of narrow angle glaucoma that would preclude use of antimuscarinic medication.
 5. Volunteer has been immunized for any botulinum toxin serotype.
 6. Volunteer has a history or current diagnosis of bladder cancer or has urine cytology results which may indicate bladder cancer not ruled out by investigator at Randomization/Day 1. Suspicious urine cytology abnormalities require the investigator's assessment to ensure that the findings are not indicative of malignancy.
 7. Volunteer is male with previous or current diagnosis of prostate cancer PSA level > 10.0 ng/mL. Volunteers with a PSA level equal to or greater than 4.0 ng/mL and equal to or less than 10.0 ng/mL must have prostate cancer ruled out to the satisfaction of the investigator according to local site practice. PSA age to be checked is on male patients 50 years or older, unless has a family history of prostate cancer or is of African American descent then PSA age to be checked is at age 40 years old.
 8. Volunteer has 24 hour total volume voided/catheterized more than 3000 mL of urine determined by completion of bladder diary collected over one consecutive 24 hour period during the 7 day diary collection period prior to Randomization/Day1.
 9. Volunteer has an active genital infection, other than genital warts, either concurrently or within 4 weeks prior to screening.
 10. Volunteer uses any anti-platelet or anticoagulant therapy or is using medications with anticoagulative effects within 3 days prior to treatment. Some medications may need to be withheld for more than 3 days per clinical judgment of the investigator.
 11. Volunteer has hemophilia or other clotting factor deficiencies or disorders that cause bleeding diatheses.
 12. Volunteer has had concurrent treatment or treatment within 6 months of Randomization/Day 1 with capsaicin or resiniferatoxin.
 13. Volunteer is currently using or plans to use an implanted or non-implantable electrostimulation/neuromodulation device for treatment of overactive bladder.
 14. Volunteer has a known allergy or sensitivity to any components of the study medication, anesthetics or antibiotics or any other products associated with the treatment and general study procedures.
 15. Volunteer has any medical condition that may put the volunteer at increased risk with exposure to ONAboNT-A including diagnosed myasthenia gravis, Eaton-Lambert syndrome or amyotrophic lateral sclerosis.
 16. Volunteer is female and pregnant, nursing or planning a pregnancy during the study, or of childbearing potential and unable or unwilling to use a reliable form of contraception during the study.

17. Volunteer is currently or has previously participated in another therapeutic drug or device study within 30 days of screening.
18. Volunteer has any condition or situation which, in the investigator's opinion, puts the volunteer at significant risk, could confound the study results, or may interfere significantly with the volunteer's participation in the study.

8. RECRUITMENT PROCESS

The volunteers will be identified from the Spinal Cord Injury or the Urology Clinic at TIRR Memorial Hermann. They will be initially approached by their spinal cord injury or urology clinic physicians for recruitment into the study. If they wish to participate in this study, they will then be approached by Dr. Smith or his research staff. The study will be published on the BCM clinical trials websites. BCM's site is <http://www.bcm.edu/clinicalstudies/?PMID=7201>. The study will also be listed on ClinicalTrials.gov.

Advertising brochures will be placed in the Urology and SCI Clinics and included in a mail out planned for potential subjects. An advertisement will be placed on the Craig's List website.

9. INFORMED CONSENT PROCESS (See APPENDIX I)

Volunteers will be informed both verbally and in written form of the study and procedures involved and be given adequate opportunity to read it and discuss with family before it is signed. The PI and designated study staff will obtain a signed/dated Informed Consent Document (ICD) before enrolling each volunteer. The original signed/dated ICD will be kept with the research study documents, a copy will be given to the volunteer, and a copy will be placed in the volunteer's electronic medical record. The subjects consented at TIRR will have their ICDs scanned into a Master File located on a server that is managed and protected by the BCM IT department. The BCM's ICD provides a signature line for a volunteer's Legally Authorized Representative if applicable. Each patient executing an informed consent document will be given a unique consecutive number beginning with the number 001.

For children ages 15 through 17 years old, assent will be obtained by adding "If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this, you also note that your child understands and agrees to take part in this study according to his or her understanding." to the adult consent form.

10. STUDY PROCEDURES (See APPENDIX II)

10.1 Screening - Visit 1

After informed consent is obtained, the following will occur at least 2 weeks but not more than 4 weeks prior to randomization/treatment:

- Inclusion/Exclusion criteria
- History and Physical Exam, including vital signs, weight
- Assessment of concurrent medications/procedures
- Kidney ultrasound or results of exam conducted within 1 year of enrollment
- Post void residual (PVR) in volunteers who micturate or have a mixed catheterization/micturition pattern

- Urine specimen to conduct urinalysis, urine culture and sensitivity
- CBC (Complete Blood Count)
- CMP (Complete Metabolic Panel)
- Pregnancy test - serum (for females only)
- Prostate specific antigen (for males only) PSA age to be checked is on male patients 50 years or older, unless has a family history of prostate cancer or is of African American decent then PSA age to be checked is at age 40 years old.
- OAB-Patient Satisfaction with Treatment Questionnaire (OAB_PSTQ)
- Urodynamic studies (if not performed 1 year prior to the Randomization Visit): This procedure measures bladder function. Lubricated catheters with pressure sensors are placed through the urethra into the bladder under sterile conditions and into the rectum.

The volunteer will then be placed in the sitting position and the pressure transducers will be leveled with the pubic symphysis.

The pressures bladder (Pves) and rectum (Pabd) are measured while the bladder is filled with saline at 40ml/min. The urodynamic machine will also record the subtracted detrusor pressure ($P_{det} = P_{ves} - P_{abd}$). Where the Pabd pressure is adjusted at baseline to render $P_{det} = 0$ by manipulation of the amount of fluid in the rectal balloon. The study will be performed following the guidelines of good urodynamics practices from the International continence society [Schafer et al, 2202; Paralyzed Veterans of America/Consortium for Spinal Cord Medicine, 2001].

The volunteer will be asked to perform several maneuvers during the procedure. These include:

- 1) Coughing (or bearing-down) several times during this procedure to make sure the equipment is working properly
- 2) Trying to suppress overactive bladder contractions, if present with sensation to stop voiding during the contractions.
- 3) To tell the urodynamicist when the bladder is maximally full.

The urodynamic study will take about 20-30 minutes to complete, with about 20 - 30 minutes of additional setup time.

Urodynamic parameters measured are baseline pressure, volume at first involuntary detrusor contraction, Peak detrusor pressure during first involuntary detrusor contraction, Maximum cystometric capacity, end fill pressure at maximum cystometric capacity or at the involuntary detrusor contraction used to determine maximum cystometric capacity and detrusor compliance.

- Volunteers will be instructed to complete a bladder diary for 7 consecutive days prior to next visit (Appendix IV)
- Dispense an antibiotic [Bactrim DS 1 tab twice a day] with instructions to take for 3 days prior to treatment (Day 1), on Day 1, and for 3 days following treatment day (total of 7 days). If subject has an allergy to sulfa or if urine culture indicates Bactrim resistant, another drug may be substituted.
- Volunteers will be instructed to stop taking medications for overactive bladder symptoms two weeks prior to injection.

10.2. Study Procedures/Study Interventions

10.2.1. Randomization and Treatment -Visit 2 (14 days to 6 weeks from Visit 1)

Volunteers will be reviewed for eligibility criteria. The following assessments will take place prior to randomization:

- Vital signs
- Urine Pregnancy test (for females only). If positive, a serum pregnancy test will be conducted to confirm.
- Urinalysis
- Post void residual in volunteers who micturate or have a mixed catheterization/micturition pattern
- Confirmation that overactive bladder medications were not taken 2 weeks prior to this visit.
- Assessment of concurrent procedures/medications, and adverse events
- Review of bladder diary
- Antibiotic drug accountability to assess compliance in taking of antibiotics

Volunteers will then be randomized to one of the two treatment groups. The following activities will take place prior to treatment:

- Urine collection for biomarker assessment
- Incontinence Quality of Life Instrument (I-QOL) and Incontinence Quality of Life Instrument (I-QOL) neurogenic module questionnaires will be completed. (See APPENDICES V-VIII: Questionnaires)

After randomization, the following events will occur:

- Bladder injection (with ONAboNT-A or saline) and initiation of oral therapy (with oxybutynin ER or placebo).
- All volunteers will be observed for at least 30 minutes after treatment prior to discharge.
- Volunteers will be instructed to continue oral antibiotics for 3 days.
- All volunteers will be instructed to complete a bladder diary for 7 consecutive days in the week prior to next visit.

10.2.1.1 Injection Procedures

10.2.1.1.a. Treatment Allocation, Use and Preparation

Volunteers will receive either ONAboNT-A 200 U or saline injection according to randomization to treatment sequence. Drug will be reconstituted/prepared by the investigational pharmacist at TIRR.

10.2.1.1.b. Administration

10.1.1.1.b.1. Study Treatment Anesthesia

The use of anesthesia during the injection procedure is determined by the investigator based on the medical need of the volunteer (e.g., tolerance to the procedure, spasticity, risk of autonomic

dysreflexia, etc.). Preventative measures regarding autonomic dysreflexia are permitted per local site practice.

The following options are permitted:

- No anesthesia
- Local anesthesia: instillation of the bladder with 1-2% lidocaine (or similar acting agent) for at least 15 minutes in order to achieve sufficient anesthesia in patients with sensate bladders or at risk for autonomic dysreflexia.
- Prior to treatment administration, the bladder should be drained of lidocaine, rinsed with saline and drained again
- Sedation may also be administered according to local site practice if deemed medically necessary
- General anesthesia: general anesthesia may be used according to local site practice by an appropriately qualified anesthesiologist. However, the use of neuromuscular blocking agents is not permitted.

10.2.2. Treatment Procedure

- The investigator should confirm that the volunteer has taken their pretreatment antibiotics as specified.
- Laboratory results must be reviewed and evaluated by the investigator indicating that they were found to be acceptable prior to treatment, including a negative serum pregnancy test for women of childbearing potential. Volunteers should continue to meet inclusion and exclusion criteria.
- Questionnaires must be completed prior to treatment.
- A flexible or rigid cystoscope may be used for study treatment injections. The bladder should be instilled with a sufficient amount of saline in order to achieve adequate visualization for the study injections.
- The investigator will receive 2 identically appearing syringes pre-filled with approximately 10 mL each of reconstituted study medication (200 U of ONAboNT-A in 20ml of preservative free saline or 20 ml preservative free saline) from the independent reconstitutor. The first syringe should be attached to the injection needle. The injection needle can then be inserted into the injection port of the cystoscope for detrusor injections. Under direct visualization, injections should be distributed evenly across the detrusor walls spaced approximately 1 cm apart to include the trigone. The needle should be inserted approximately 2 mm into the detrusor for injections. The entire 20 mL will be administered as 20 injections each of 1 mL (total volume administered is 20 mL), evenly distributed into the detrusor via cystoscopy. The injection process will take approximately 15 minutes to complete. After the treatment is finished, the patient will remain in the clinic for at least 30 minutes for observation. Also, he/she will be asked to urinate before leaving the office. If the patient cannot satisfactorily urinate to empty his/her bladder [i.e. urinary retention], a temporary catheter may be used to drain the bladder. (See APPENDIX IX: Injection Pattern Diagram)
- All volunteers must be observed for at least 30 minutes following the study treatment administration. Safety monitoring and assessments are to be done according to local site practice (e.g., monitoring of blood pressure, pulse rate and ensuring that volunteer has emptied the bladder before leaving the site).
- Spinal cord injury volunteers with lesions above the T6 level are particularly at risk of developing autonomic dysreflexia, which presents with symptoms of increased blood

pressure, relative bradycardia, headache, and skin flushing [Blackmer, 2003]. Should autonomic dysreflexia develop in a volunteer, the condition should be immediately handled according to local site practice. An occurrence of autonomic dysreflexia during study drug administration will be reported as an adverse event. Guidelines for managing autonomic dysreflexia will be included in the Investigator Binder [Paralyzed Veterans of America/Consortium for Spinal Cord Medicine, 2001].

- Volunteers should be instructed to contact the study site if they experience any adverse events post-treatment.

10.3 Post Randomization/Treatment Visits (Follow Up) -Day 3, and Weeks 4, 12, and 24 (\pm 3 days) post randomization/treatment

10.3.1 Visit 3: Day 3 to 5 post randomization/treatment (Telephone Visit)

Discuss subject's well-being, concomitant medications, antibiotic compliance, and side-effects or adverse events.

10.3.2 Visits 4: Week 4 (\pm 3 days) post randomization/treatment

- Vital Signs
- PVR for volunteers who micturate or have a mixed catheterization/micturition pattern
- Urine collection for biomarker assessment
- Urinalysis, culture and sensitivity
- Collect bladder diary for Total Volume Voided assessment
- Collect oral study drug pill bottle.
- Urine pregnancy test (females). If positive, a serum pregnancy test will be conducted to confirm.
- Concurrent medications and procedures
- Adverse events assessment
- The I-QOL), (I-QOL) neurogenic module, OAB-Patient Satisfaction with Treatment Questionnaire (OAB_PSTQ), and Patient Global Assessment (PGA) questionnaires will be completed.
- Volunteer will be instructed to complete a bladder diary for 7 consecutive days in the week prior to next visit.
- Dispense oral study medicine with instructions to bring all unused medicine to next visit.

10.3.3. Visit 5: Week 12 (\pm 3 days) post randomization/treatment

- Same events and procedures as previous study visits plus urodynamic studies.

10.3.4. Visit 6: Week 24 (\pm 3 days) post randomization/treatment - End of Study Visit

- Physical Exam, including vital signs
- CMP (Complete Metabolic Panel)
- PVR for volunteers who micturate or have a mixed catheterization/micturition pattern
- Urine collection for urinalysis, culture and sensitivity, and biomarker assessment
- Study drug accountability
- Collect bladder diary

- Serum pregnancy test (females)
- Concurrent medications and procedures
- Adverse events assessment
- Questionnaires = I-QOL, I-QOL-Neurogenic Module, OAB-PSTQ, PGA

11. SAMPLE SIZE JUSTIFICATION

Data from a preliminary study in SCI patients showed that Ditropan XL (i.e. oxybutynin ER equivalent) reduced weekly urinary incontinence episodes at 12 weeks by 54% (i.e. from 13 to 6 per week).[Bennett et al., 2004] A second large randomized trial found that oxybutynin lowered incontinence episodes from 3.3 to 2 (i.e. 39%) after 21 days of treatment.[Stohrer et al, 2007] The most recent and largest efficacy and safety study demonstrated that ONAboNT-A reduced weekly urinary incontinence episodes by 69% at 6 weeks (i.e. from 30.5 to 9.5 per week). [Ginsberg et al, 2011] Our patient population will consist of patients having a relatively high number of weekly urinary incontinent episodes, similar to those in the Ginsberg study. Although our study groups will include a placebo pill and sham injection group we don't expect to see a significant placebo effect in our neurogenic bladder population as has been previously demonstrated in idiopathic (i.e. non-neurogenic) overactive bladder populations. For this study, we will assume a reduction of 69% in incontinence episodes for the ONAboNT-A group and a 45% reduction in the oxybutynin group (i.e. a value midway between the results of Bennett et al, 2004 and Stöhrer et al, 2007).

Our sample size assumptions include a mean baseline level of 30 weekly incontinent episodes, a 69% reduction of incontinent episodes in the ONAboNT-A + placebo pill group (i.e. post-treatment 9 incontinent episodes), a 45% reduction in the oxybutynin + sham injection group (i.e. post-treatment 17 incontinent episodes) at 12 weeks, an alpha level of 0.05, 80% power and a standard deviation of 50% of the mean. The resulting sample size of 18 subjects per group (total=36) is adjusted for an expected attrition of 20%. This effect was selected as the smallest effect that would be important to detect, in the sense that any smaller effect would not be of clinical or substantive significance. It is also assumed that this effect size is reasonable, in the sense that an effect of this magnitude could be anticipated based on previous findings.

12. DATA ANALYSIS

Initially, graphical methods will be used to assess distributional properties of the data (weekly urge incontinent episodes, urine biomarker levels, quality of life scores) and to examine patterns of correlations between observations at different time points. Measures such as age, gender, number of weekly urinary incontinence episodes, urine biomarker levels, I-QOL and I-QOL neurogenic questionnaires and disease severity will be examined using summary statistics to determine if any baseline differences exist between the 2 study groups. If extreme departures from normality are found, non-parametric methods such as the Wilcoxon rank-sum test or transformation of the data will be considered. Questionnaire scores will be examined for reliability using Cronbach's alpha. The distributions of the scores will be examined to see if they are evenly distributed around the mid-point of the scales or are clustered at the top or bottom of the scales (ceiling or floor effect). If strong ceiling or floor effects are found, this could limit the usefulness of these measures.

The primary endpoint is the reduction in mean weekly incontinent episodes in the ONAboNT-A treated group compared to the oxybutynin treated group at 12 weeks. The change between the 2 groups at 12 weeks will be analyzed using a general linear model approach with weekly

urinary incontinent episodes as the outcome variable, treatment group as the independent variable with adjustment for baseline weekly urinary incontinent episodes, a baseline covariate. This approach is equivalent to the independent t-test, but allows adjustment for the baseline outcome levels. Exploratory growth curve analysis will be done to investigate the pattern (linear, quadratic or possibly cubic) of change in incontinence episodes over time during the entire data collection period. Growth curve models have an assumption for multivariate normality of the dependent variables. If the data are not normally distributed but approximately follow some exponential distribution, then a generalized linear model using a generalized estimating equation can be applied. The generalized estimating equation links functions to allow maximum likelihood estimation for variables that follow a distribution from the exponential family other than the normal. [McCullagh and Nelder, 1989] The same hypotheses can be tested with these methods as with the normal growth curve model.

Secondary endpoints, such as quality of life scales, will be tabulated using cross tabulations and summary statistics. Measures of association such as chi-square and correlations will be used to assess differences in relationships between the control and intervention groups. Changes in these secondary measures between control and intervention groups at 12 weeks will be compared using independent t-tests or the Wilcoxon rank-sum test. Additionally, we will look at the longitudinal pattern of the questionnaires at baseline, 4, and 12 weeks using growth curve modeling to explore the trajectory of change. Statistical analysis will be done using SAS, version 9.2 software.

13. ENDPOINTS

The **Primary Endpoint** is the mean reduction in weekly incontinence episodes 12 weeks following treatment. **Secondary Endpoints** include improvements in quality of life scales (Incontinence Quality of Life Instrument (I-QOL), Incontinence Quality of Life Instrument Neurogenic Module, OAB-Patient Satisfaction with Treatment Questionnaire (OAB_PSTQ), and Patient Global Assessment (PGA), changes in maximum capacity by urodynamic study, as well as reductions in urine NGF and chemokine/cytokine levels (pg/ml normalized to creatinine). We will also correlate NGF and chemokine/cytokine levels with disease severity and treatment outcome. Other endpoints include detrusor compliance (DC) (ml/cm H₂O) by urodynamics, total volume voided recorded over one 24 hour period as recorded on bladder diary for all voids (catheterization and voluntary), and number of episodes per day of voiding and method (catheterization and voluntary) as recorded by bladder diary, and the frequency of asymptomatic bacteriuria (i.e. ASB) versus symptomatic UTI's. We will correlate NGF and chemokine/cytokine levels with disease severity, the presence of ASB versus symptomatic UTI, and treatment outcome.

14. LABORATORY EVALUATIONS

14.1. Specimens

Urinary levels of NGF, cytokines and chemokines will be measured at study visits 2, 4, 5, and 6. Urine will be collected by sterile catheter or clean catch midstream (CCMS) voided specimen. Specimens will be processed at the time of collection, de-identified with an untraceable number, and shipped to the Urology Research laboratory at William Beaumont Hospital, Royal Oak, MI, under the direction of Michael B. Chancellor, MD. The identification number will be used in research documents.

14.2 Specimen Preparation, Evaluation, and Analysis

The Urology Laboratory Manual (Appendix II) will provide specific information.

14.3. Confidentiality

The data will be stored with Dr. Chancellor in a locked office. Urine will only be identified by volunteer identification number and initials prior to shipping. Dr. Chancellor will not have access to any other patient identifiers. The urine will be placed into a minus 80 freezer in the locked urology research laboratory with restricted access to the Research Institute.

To ensure rigorous HIPPA compliance throughout the study, each urine specimen from the volunteers enrolled in the study will be stored in the urology biobank, which will de-identify the specimens with an untraceable number upon receiving the specimen to delink the volunteer clinical data from analysis team. This number will be used in research documents. All data will be stored in Dr. Chancellor locked office. The key to urine biobank number and volunteer identification number is held in Urology research office accessible only to Dr. Chancellor.

The risks from breach of confidentiality will be minimized by using de-identified volunteer specimens and the secured computer database maintained in the urology biobank will protect the identity of volunteers from the analytic team.

After research testing required for this study is completed, the remaining portion of urine samples will be stripped of the code and will be banked for future use. It will be kept until it is all gone. Samples will not be sold or transferred to anyone else. If at any time the subject withdraws from this study he will not be able to get his urine samples back because there is no identifying information on the samples.

15. DATA COLLECTION AND MANAGEMENT

15.1. Methods for Data Collection

Protocol-specific data will be collected on Case Report Forms and forwarded to the biostatistician for compilation by the data manager. The completed dataset is available to the investigators and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from BCM. (See APPENDIX XI: Case Report Forms)

15.2. Volunteer Identifiers

An unambiguous volunteer identification code will be used in lieu of the volunteer's name on all study data compiled. This volunteer identification code will include the volunteers' initials and volunteer number. A key for this code will be maintained by the Principal Investigator and kept separate from study files. All source documents and study data will be kept confidential. Study data will be kept in a locked file cabinet and/or password protected and encrypted computers and stored on servers managed by BCM IT.

15.3. Confidentiality

15.3.1 Baylor College of Medicine (BCM) and TIRR Memorial Hermann

The PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

Research data will be maintained by Dr. Smith in his office in the Baylor Urology Clinic.

Regulatory documents will be managed by Research Administration of the Scott Department of Urology, BCM located in 502/506D in the Jewish Wing of Main Baylor. The Faculty Center suite utilizes an electronic locking system for security purposes. The Main Baylor offices have keyed entries. All computers utilized for this study are password protected and encrypted. Data is stored on encrypted BCM servers that are managed by IT.

The BCM Scott Department of Urology complies fully with the HIPAA Privacy Rule.

Regulatory authorities that provide oversight of this clinical trial include IRBs, OHRP, and any other applicable state and local authorities will have access to the study data.

15.3.2. William Beaumont Hospital

All specimens will be shipped to the laboratory with only volunteers' initials and volunteer ID# as identifications. Dr. Chancellor will not have access to the key code list of volunteers.

15.4. Disposition of Data

To enable evaluations and/or audits from Health Authorities/BCM, the investigators agree to keep records, including the identity of all participating volunteers (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all CRF's, and detailed records of drug disposition. The requirements of the IRB will also be met.

15.5. Sharing Study Results

Volunteers may never be able to obtain limited research health information.

16. RISK/BENEFITS ASSESSMENT

16.1. Foreseeable Risks:

16.1.1. ONAboNT-A

It is expected that some participants may have some or all of the following side effects when given ONAboNT-A. Other side effects may occur which were not seen before. Side effects are usually temporary and manageable. However, it is possible they could cause serious disease or death. The study may include risks that are unknown at this time.

Based on the results of the experimental testing in animals, there may have an increased risk of development of bladder stones.

There have been rare reports of serious and/or immediate or even deadly abnormally sensitive reactions after treatment with ONAboNT-A. These reactions include allergic reaction, skin rash, itching, swelling, and difficulty in breathing.

It is a rare possibility that the injection of ONAboNT-A could lead to botulism. The classic symptoms of botulism include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. The doctor's examination may reveal that the gag reflex and the deep tendon reflexes like the knee jerk are decreased or absent.

There have been rare reports of sudden death, sometimes associated with difficulty in swallowing or pneumonia. There have also been rare reports of heart problems (including irregular heartbeats and heart attack, some resulting in death). Some of these patients were already at risk for heart disease. It is not known if ONAboNT-A actually caused these problems.

It should not be used when infection is present at the injection site or in people known to be abnormally sensitive to ONAboNT-A.

The following events have been observed since it has been marketed: skin rash, itching, and allergic reaction. In general, these side effects occur within the first week following injection and, while usually temporary, they may last several months. Pain, tenderness, or bruising around the injection site may also occur. Local weakness of the injected muscle(s) is expected. Weakness of nearby muscles may also occur due to spread of ONAboNT-A.

BOTOX contains albumin, which comes from human blood. Although the blood is rigorously tested, there is an extremely remote risk for the transmission of viruses and similar infectious agents.

16.1.2. Oxybutynin ER: Also known as Ditropan XL

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that Oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

Common Side Effects: Blurred vision; constipation; diarrhea; dizziness; drowsiness; dry eyes, nose, skin, or mouth; headache; indigestion; nausea; runny nose; stomach pain or upset; trouble sleeping; weakness

Severe Side Effects: Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); confusion; difficult or painful urination; fast or irregular heartbeat; fever; hallucinations; mental or mood changes (e.g., agitation); seizures; swelling of the hands, ankles, or feet; vision problems.

Oxybutynin chloride is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin chloride is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

The concomitant use of Oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects. If side effects occur, they will be managed as effectively as possible.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index.

The safety of Oxybutynin chloride administered to women who are or who may become pregnant or are breastfeeding has not been established. Therefore, Oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

16.1.3. Placebo

Since placebo has no active drug, the medical condition may become worse, stay the same or improve.

16.1.4. Antibiotics (CIPRO, or generic, 500 mg twice a day)

The most frequent side effects of ciprofloxacin include nausea, vomiting, diarrhea, abdominal pain, rash, headache, and restlessness. Rare allergic reactions have been described, such as hives and anaphylaxis (shock).

16.1.5. Cystoscopy with Bladder Injection

The discomfort is nearly identical to being catheterized, which generally causes slight to moderate discomfort. There will be a feeling of fullness in the bladder and a sensation to empty during the cystoscopy examination. Bleeding, infection, damage to urethra or surrounding structures may occur.

16.1.6. PVR

The risks of having a catheter placed in the bladder for draining the residual urine are infection of the urinary tract, injury to the urethra caused by rough insertion of the catheter, narrowing of the urethra due to scar tissue caused by the insertion of a catheter, injury to the bladder caused by incorrect insertion of the catheter.

16.1.7. Urodynamics

Generally the risks of a urodynamic study are low and are no more than those of a Foley Catheter insertion, which include the possibility of infection, trauma to the urethra or prostate,

traumatic bleeding from the catheterization, discovery of previously unsuspected urethral stricture with inability to get the urodynamics catheter into the bladder.

Patients with a spinal cord injury generally occurring at the Thoracic 5 (T-5) level and above have a risk of experiencing autonomic dysreflexia during bladder filling during the urodynamic or study treatment procedures. To minimize this risk continuous blood pressure monitoring is performed throughout the study.

Autonomic dysreflexia can develop suddenly, and is a possible emergency situation. Symptoms of autonomic dysreflexia include the following: elevation in blood pressure, headache, goose pimples, sweating above the level of injury, nasal congestion, slow pulse, blotching of the skin, and restlessness. If not treated promptly and correctly, it may lead to seizures, stroke, and in some cases, even death.

16.1.8. Ultrasound

Ultrasound testing is painless and harmless but the volunteer might experience anxiety in anticipation of the test. Ultrasound tests involve no radiation and studies have not revealed any adverse effects.

16.1.9. Blood draw

Inserting needles into veins for collecting blood may be uncomfortable. Risks include slight bruising at the puncture site, fainting, the formation of a small blood clot or swelling of the vein and surrounding tissue, bleeding from the site, and the remote possibility of infection at the site of the needle puncture. Fainting is usually harmless, of short duration, and typically produces feelings of weakness, sweating, slowing of the heart rate and an abnormal decrease in blood pressure. Care will be taken to avoid these complications.

16.1.10. Questionnaires

Completing the questionnaires may cause you to have or to experience some level of emotional discomfort due to the personal nature of the questions. The study doctor and staff will maintain a professional and caring attitude while administering the questionnaires.

16.1.11. Confidentiality

The loss of confidentiality regarding research information is a possibility, although, the risk is extremely small. The investigator and his staff will make every effort to maintain the confidentiality.

16.1.12. Pregnancy

It is possible that the medicines used in this study could injure a fetus if volunteer or volunteer's partner becomes pregnant while taking them. Pregnant and/or lactating women will be excluded from the study. As outlined in the protocol, women of childbearing potential will be carefully screened with serum pregnancy testing within 48-72 hours prior to randomization and each treatment (s). Because of the potential risks involved, pregnancy should not occur during participation in this study. The following methods of contraception, if properly used, are generally considered reliable for females of childbearing potential who may participate in the study: oral contraceptives, patch contraceptives, injection contraceptives, male condom with

intravaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation), vasectomized partner(s), or total sexual abstinence.

16.2. Risk Management and Emergency Response

16.2.1. Safety Measures

The following safety measures are included in the protocol in an effort to eliminate risks to volunteers:

- Physical examination
- Vital signs
- Urinalysis
- Urine culture and sensitivity
- Kidney ultrasound
- Post void residual (PVR) by bladder scan, ultrasound, or catheterization for volunteers who micturate or have a mixed catheterization/micturition pattern
- Serum pregnancy test for female volunteers of childbearing potential at screening, qualification for re-treatment if urine pregnancy is positive, and study exit
- Urine pregnancy test for female volunteers of childbearing potential on day of treatment (prior to each treatment). If positive, a serum pregnancy test will be conducted to confirm.
- Concurrent medications
- Concurrent procedures
- Serious medical events
- Adverse events

16.2.2. Health outcome measures

- Incontinence Quality of Life Instrument (I-QOL) [Patrick et al, 1999]: The I-QOL is a disease-specific, quality of life (QOL) questionnaire designed to measure QOL impact of urinary incontinence on volunteers. Designed for self-completion, the I-QOL takes approximately 5 minutes to complete. The I-QOL is scored as a total score, and 3 domain scores of Avoidance Limiting Behavior, Psychosocial Impact, and Social Embarrassment.
- Incontinence Quality of Life Instrument Neurogenic Module [Lee et al, 2005]: The I-QOL Neurogenic Module is designed to measure the impact of urinary incontinence on volunteer's lives in a neurogenic population.
- OAB Patient Satisfaction with Treatment Questionnaire (OAB-PSTQ): The OAB-PSTQ is a volunteer satisfaction with treatment questionnaire created by Allergan, Inc. Volunteers' goals and expectations from treatment are assessed.
- Patient Global Assessment (PGA): The PGA is a global volunteer assessment that assesses the volunteer's symptoms, quality of life, activity limitations and overall emotions.

16.2.3. Stopping Criteria

If moderate to severe adverse events occur after an injection of ONAboNT-A, then no further injection will be given. If moderate to severe adverse events occur due to the Oxybutynin, the medication will be stopped. Volunteers will be symptomatically treated and closely monitored after any moderate to severe adverse events.

In the event of an emergency, the research pharmacy will provide the unblinded information for the volunteer. Care will be provided to the volunteer at the VA Medical facility.

16.3. Potential benefits

Approximately 25 million Americans suffer from varying degrees of urinary incontinence with many of these being caused by neurogenic detrusor overactivity (NDO) in spinal cord injured patients. Antimuscarinic drugs, while effective in many patients, have significant adverse events like dry mouth, constipation, and blurred vision that limit their utility. The potential benefits to the volunteer include improvement in the urinary incontinence symptoms, reduction in the rate of urinary tract infections, decrease in the number of required catheterizations, and an ease of the financial burden of buying protective garments.

The potential benefits to society in addition to those mentioned above would include the decrease in medical costs.

16.4. Intent to benefit

For volunteers that cannot give their own consent to participate in this study, an intent to benefit will be promulgated by the fact that each participant will be given the opportunity to receive ONAboNT-A injection after completing the study as standard of care for refractory NDO. We expect that ONAboNT-A will reduce urinary incontinence as well as its associated complications within our patient cohort.

16.5. Study-Related Injury

If any side effect or injury should occur, the participant should notify Dr. Smith at 713-798-4001 so that he can provide directs on how to receive appropriate medical treatment.

Research personnel will try to reduce, control, and treat any complications from this research. If a participant is injured because of this study, the participant or third party insurer is responsible for the medical care that is provided just like any other medical care.

17. WITHDRAWAL FROM THE PROTOCOL

Volunteers may discontinue participation in the study at any time without penalty or loss of benefits to which the volunteer is otherwise entitled. If possible, a volunteer who is withdrawing should complete the End of Study visit events/procedures. Volunteers participating in this study will receive \$50 for completing each of the study visits 2, 4, 5, and 6.

18. MODIFICATIONS TO THE PROTOCOL

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by BCM. Each amendment must be approved by all the principal investigators and each IRB, and if applicable, the local regulatory authority. Local requirements must be followed. If a protocol amendment requires a change to the Written Informed Consent Form, approval of the revised Written Informed Consent Form by the IRB is required before the revised form is used. The principal investigator is responsible for the distribution of these documents to his study staff and to appropriate institutional review committees.

Examples of amendments requiring such approval are:

- increases in drug dose or duration of exposure of volunteers,
- significant changes in the study design (e.g. addition or deletion of a control group),
- increases in the number of invasive procedures,
- addition or deletion of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all volunteers included in the trial. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

Changes in the staff used to monitor trials
Minor changes in the packaging or labeling of study drug
Revisions to study forms

Any deviation to the protocol that may have an effect on the safety or rights of the volunteer or the integrity of the study must be promptly reported to the IRB and other required authorities. A deviation log will be maintained by the site. The log will be tabulated into a master log and submitted with each annual IRB renewal report.

19. REPORTING UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS/ OTHERS

Reporting of unanticipated problems will be in accordance to the current IRB guidelines and FDA regulations.

An adverse event log will be maintained at the clinical site. The logs will be tabulated into a master log and submitted with each annual IRB renewal report.

20. CONTINUING REVIEW AND FINAL REPORT

Annual IRB review submissions will be made according to the local IRB's guidelines and a final report will be submitted at the completion of the study. All approvals and/or communications between the IRB and site will be forwarded to the HRPO, and any additional authorities providing oversight of this study.

21. SURVEYS, QUESTIONNAIRES, AND OTHER DATA COLLECTION INSTRUMENTS

21.1. Informed Consent Document (ICD)

Each potential volunteer will review the informed consent document with the study personnel. If the potential volunteer is willing to participate and comply with the study's requirements, the ICD will be executed.

21.2. Voiding Diary

Volunteers will complete the Voiding Diary for 7 consecutive days in the week prior to their clinic visits.

21.3. Questionnaires

Volunteers will be requested to complete the following questionnaires:

21.3.1. Incontinence Quality of Life Instrument (I-QOL) [Patrick et al, 1999]:

The I-QOL is a disease-specific, quality of life (QOL) questionnaire designed to measure QOL impact of urinary incontinence on volunteers. Designed for self-completion, the I-QOL takes approximately 5 minutes to complete. The I-QOL is scored as a total score, and 3 domain scores of Avoidance Limiting Behavior, Psychosocial Impact, and Social Embarrassment.

21.3.2. Incontinence Quality of Life Instrument Neurogenic Module [Lee et al, 2005]

The I-QOL Neurogenic Module is designed to measure the impact of urinary incontinence on volunteer's lives in a neurogenic population.

21.3.3. OAB Patient Satisfaction with Treatment Questionnaire (OAB-PSTQ)

The OAB-PSTQ is a volunteer satisfaction with treatment questionnaire created by Allergan, Inc. Volunteers' goals and expectations from treatment are assessed.

21.3.4. Patient Global Assessment (PGA)

The PGA is a global volunteer assessment that assesses the volunteer's symptoms, quality of life, activity limitations and overall emotions.

21.4. Case Report Forms (CRFs)

Protocol-specific data will be collected on Case Report Forms as required. The completed dataset is available to all the investigators, is the sole property of BCM, and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from BCM.

22. REFERENCES CITED

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APPENDIX I

SCHEDULE OF EVENTS

Schedule of Events

Events/Procedures	Consent/ Screening	Treatment and F-U Sequence				
	Visit 1 2 to 4 weeks prior to Visit 2	Visit 2 Randomization and Injection Day 1 V 1 +14 Days to 6 Weeks	Visit 3 Telephone 3-5 Days Post-Injection	Visit 4 4 wks Post-injection ± 3 days	Visit 5 12 wks Post-injection ± 3 days	Visit 6 End of Study 24 wks Post-injection ± 3 days
Consent	X					
Inclusion/exclusion	X	X				
Concomitant medications	X	X	X	X	X	X
Physical exam	X					X
Vital signs	X	X		X	X	X
Weight	X					
CBC	X					
CMP	X					X
PSA (Males Only)	X**					
Serum Pregnancy test (Females)	X	X*		X*	X*	X
Urine Pregnancy test (Females)		X		X	X	
Post void residual	X	X		X	X	X
Kidney ultrasound within 1 year	X					X
Urodynamic studies within 1 year	X				X	
Urinalysis	X	X		X	X	X
Urine C&S	X			X	X	X
Urine specimen collection for biomarker evaluation		X		X	X	X
Off meds for 2 weeks prior to injection		X				
Bladder diary	X	X		X	X	X
Assessment of total volume voided on diary		X		X	X	X
OnaBoNT-A/Placebo Injection		X				
Dispense Oxybutynin/Placebo		X		X	X	
Study product Accountability				X	X	X
Antibiotic prescription	X					
Antibiotic Accountability		X				
I-QOL		X		X	X	X
I-QOL neurogenic module		X		X	X	X
OAB-PSTQ	X			X	X	X
Patient Global Assessment				X	X	X
Adverse event assessments		X	X	X	X	X
Subject stipend for transportation		X		X	X	X

*Serum Pregnancy will be done if urine pregnancy is result is positive

PSA- **50 years or older, unless has a family history of prostate cancer or is of African American decent then PSA age to be checked is at age 40 years old

Non-standard of care is highlighted in yellow.

APPENDIX II

URINE COLLECTION PROTOCOL

**ONAbNT-A v. Oral Oxybutynin in Spinal
Cord Injured Patients with NDO
(#11-09-10-04)**

URINE COLLECTION PROTOCOL

URINE COLLECTION AND PROCESSING PROTOCOL

Samples should be processed immediately and submitted to William Beaumont Health System when a set of urine specimens from a batch of 10 patients or a reasonable size batch is complete:

1. Record the date, time of collection and the time you start sample processing on sample form.
2. Divide urine equally between two 50ml tubes of undiluted urine collected preferably from volunteers when they feel a full sensation or the need to catheterize will be used for analysis.
3. For the urine sample to be preserved (one of the 50 ml tubes):
4. Carefully cut the tip off the Norgen Urine Preservative Single Dose ampule and dispense the contents into one of the 50mL conical tubes with the urine sample. Tighten container lid. Invert several times to mix.
5. From the tube with urine+preservative, aliquot 5 mL into a pre-labeled tube.
6. Make sure both containers are securely closed and will not leak by carefully inverting. Tubes should have "P" on the label.
7. Wrap with parafilm the lids of both the 50mL tube and 5mL tube with preserved urine (this is done in case there is a leak).
8. Place in biohazard bag with absorbent material.
9. Store at room temperature out of direct light.
10. For the urine sample to be frozen (the other 50mL tube):
 - a. Spin the sample 10 min @ 650 x g at 4°C.
 - b. During the spin, add 10uL of BME to 1mL of Buffer SK and ensure all tubes to be used are labeled.
 - c. Pour off the supernatant carefully into a new 50mL tube as not to disturb or dislodge the cell pellet.
 - d. To cell pellet: Add 350 µL of Buffer SK with BME to the pellet. Lyse cells by vortexing for 15 seconds. Ensure that the entire pellet is completely dissolved before proceeding to the next step. Transfer the lysate to an RNase-free microcentrifuge tube. Add 200 µL of 100% ethanol to the lysate. Mix by vortexing for 10 seconds. Store at -80°C. Tube should have "RNA" on label.
 - e. To urine supernatant: Aliquot 1mL into ten (10) 1.5mL microcentrifuge tubes. Store at -80°C.
 - f. Discard any remaining urine.
4. Collection should immediately be placed on ice to halt enzymatic activity. Store on ice until processing. Process within 30 to 60 minutes or as soon as possible.
5. Ship OVERNIGHT with AM delivery in sufficient **DRY ICE** to:

Dr. Laura Lamb
William Beaumont Hospital Research Institute
3811 West 13 Mile Road
Royal Oak, MI 48073
(248) 551-6226

Contact several days before shipping:

Dr. Laura Lamb	laura.lamb@beaumont.org	248-551-0579
Sarah Bartolone	sarah.bartolone@beaumont.org	248-551-6226

Labeling of Tubes

- All tubes should have study ID number and date collected on them.
- For samples containing urine + preservative, after sample ID number put “-P” (e.g. 103-P). There will be one 50mL tube and one 5mL tube total.
- For sample containing urine + Buffer SK + BME + Ethanol, after sample ID put “RNA” (e.g. 103 RNA). There will be one 1.5mL tube total.
- For sample containing urine supernatant, no additional labeling is needed (e.g. 103). There will be ten 1.5mL tubes total.

URINE SAMPLE ACQUISITION FORM

(to be filled and submitted with each sample)

H #: 34972

Subject ID#: _____

Date of collection: _____

Time of collection: _____

Time samples were frozen: _____

Time started sample processing: _____

- Preservative added to 50ml sample: Yes No
- 5ml aliquot of preserved urine aliquoted: Yes No
- BME added to Buffer SK: Yes No
- Buffer SK +BME and Ethanol added to pellet: Yes No
- 10 aliquots of frozen urine made: Yes No
- Preserved samples stored at room temperature: Yes No
- Frozen Samples stored at -80 degrees C: Yes No

Time sample completed: _____

Any Additional Notes:

Name (Printed)

Signature

Date

APPENDIX III

VOIDING DIARY

**BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders
7-DAY DIARY**

Volunteer ID# _____ Visit # _____

The diary is to be completed for the 7 days in a row the week before your clinic visit. Write the current date and diary day in the **DATE** row for each day.

At the time you experience an accidental leakage of urine, rate the episode as follows in the **Leakage** column:

1 = damp or a few drops of urine

2 = wet your underwear or pad

3 = soaked underwear/clothes or emptied bladder. You may have several accidents during an hour. Please record each event.

In the **Void** column, place a check mark (√) each time you urinate in the toilet.

In the **CIC** column, please place a check each time you catheterize.

In the **Amount** column, indicate each time the number of ccs you urinated **OR** catheterized

DATE	TIME	Leakage	Void	CIC	Amount
10/1/10	12am-3:59am			√	175
	4am-4:59am				
	5am-5:59am				
	6am-6:59am			√	300
	7am-7:59am				
	8am-8:59am	1, 2			
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm	3, 1, 1			
	1pm-1:59pm				
	2pm-2:59pm			√	100
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm			√	200
	7pm-7:59pm				
	8pm-8:59pm	2			
	9pm-9:59pm			√	250
	10pm-10:59pm				
	11pm-11:59pm			√	150

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 1 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 2 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 3 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

1 = Damp or a few drops of urine on underwear;

2 = Wet your underwear or pad;

3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 4 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 5 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 6 of 7 DAY DIARY

Visit # _____

DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

BoNT-A vs. Oxybutynin for Spinal Cord Injuries with Overactive Bladders

DAY 7 of 7 DAY DIARY

Visit # _____

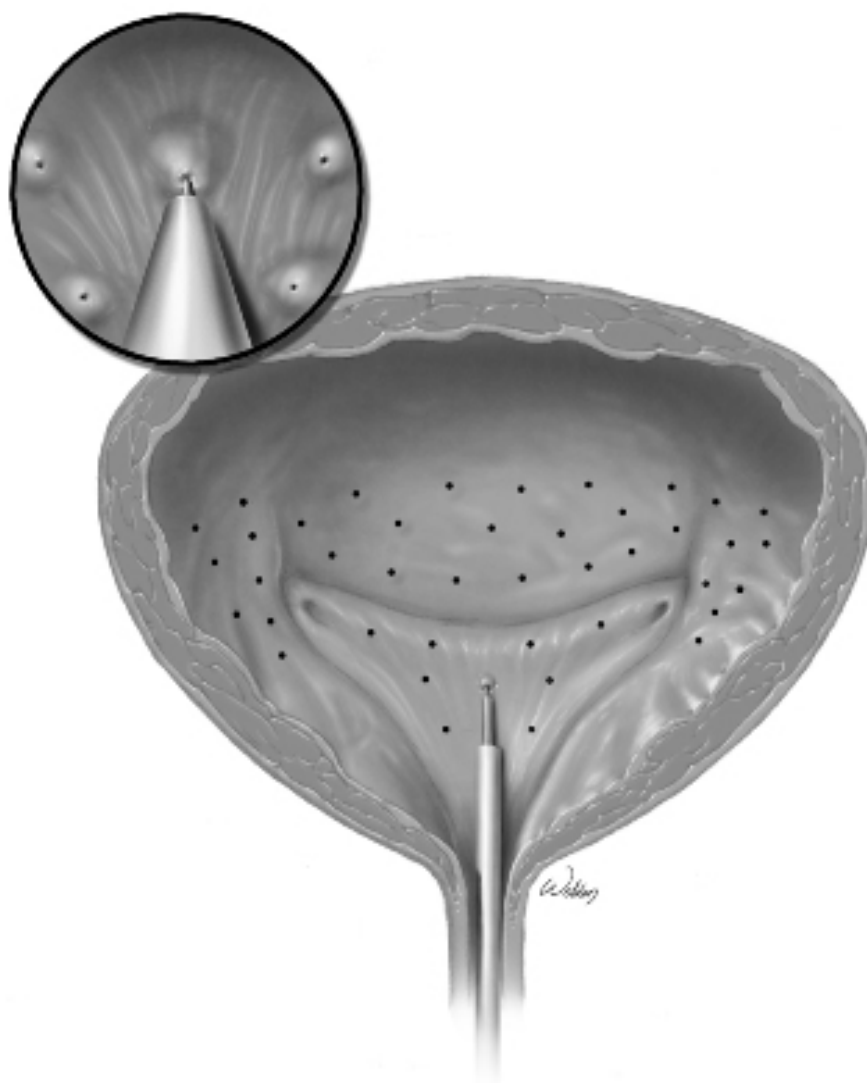
DATE	TIME	Leakage	Void	CIC	Amount
	12am-3:59am				
	4am-4:59am				
	5am-5:59am				
	6am-6:59am				
	7am-7:59am				
	8am-8:59am				
	9am-9:59am				
	10am-10:59am				
	11am-11:59am				
	12pm-4:59pm				
	1pm-1:59pm				
	2pm-2:59pm				
	3pm-3:59pm				
	4pm-4:59pm				
	5pm-5:59pm				
	6pm-6:59pm				
	7pm-7:59pm				
	8pm-8:59pm				
	9pm-9:59pm				
	10pm-10:59pm				
	11pm-11:59pm				

- 1 = Damp or a few drops of urine on underwear;
- 2 = Wet your underwear or pad;
- 3 = Soaked underwear/clothes or emptied bladder

APPENDIX IV

INJECTION DIAGRAM

INJECTION DIAGRAM



The investigator will receive 4 identically appearing syringes pre-filled with 8 mL each of reconstituted study medication (total of 32 mL) from the independent reconstitutor. The first syringe should be attached to the injection needle. 2 mL of study medication should then be used to prime the needle (resulting in a volume of 6 mL in the first dosing syringe). A total of 30 mL remains between the 4 injection syringes for study treatment administration. Each treatment session will be administered as 20 injections each of 1 mL (10u/ml), evenly distributed into the bladder. The injection needle can then be inserted into the injection port of the cystoscope for detrusor injections. Under direct visualization, injections should be distributed evenly across the detrusor walls and dome, spaced approximately 1 cm apart to include the trigone. The needle should be inserted approximately 2 mm into the detrusor for injections. The entire 30 mL will be administered as 30 injections each of 1 mL (total volume administered is 30 mL), evenly distributed into the detrusor via cystoscopy (see Injection Pattern Diagram in Appendix II). After the injections are given, the saline used for bladder wall visualization should be immediately drained. Indwelling catheters may be used during the 24-hour post-treatment period at the discretion of the investigator.

APPENDICES V

QUESTIONNAIRES

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals**RENEWAL**

Protocol Number: H-34972
Principal Investigator: CHRISTOPHER PATRICK SMITH
Initial Submit Date: 05/22/2015
Renewal Submit Date: 03/17/2017
Protocol Title: A DOUBLE-BLIND, RANDOMIZED STUDY OF THE SAFETY AND EFFICACY OF ONABOTULINUMTOXINA (ONABONT-A) VERSUS ORAL OXYBUTYNIN IN SPINAL CORD INJURED PATIENTS WITH NEUROGENIC DETRUSOR OVERACTIVITY (PROTOCOL NUMBER 11-09-10-04) (TIRR)

SUBJECTS

During your last approval period, you were approved to enroll 36 subjects locally and 36 subjects worldwide.

LOCAL: 8
WORLDWIDE: 8

MONITORED

If the study was monitored during the last approval period, please indicate by whom and provide a brief description of the findings:

Not Applicable

PROTOCOL STATUS

If the study will not be open to recruitment during the next approval period, indicate why the study should remain open:

Not Applicable

NEW INFORMATION

I am aware of no new information that might effect a subject's willingness to continue participating in this study.

GENERAL SUMMARY

All subjects were consented using the current IRB-approved consent forms to this clinical research trial prior to any study events or procedure taking place. A total of 8 subjects signed consent forms during the past year. 2 subjects screen failed. 2 subjects received treatment, 4 subjects are still in follow-up, 1 subject completed the study and 1 subject withdrew from the study. No serious adverse events were reported.

RISK/BENEFIT RATIO

The potential benefits to the subjects still outweigh the potential risks.

EVENTS

No Events have been reported.

EXCEPTIONS

No Exceptions have been reported.

DEVIATIONS

No Deviations have been reported.

AMENDMENTS (As of: 10/10/2017 8:41:09 AM) (Sort Order: Amendment Date)

Amendment Submit Date: 06/27/2017
Reason: Change Subject Population
Description: Protocol v.6/20/17 Inclusion Criteria, Section 7.1, page 16 Revised lower weight limit to 90 pounds. It is noted that the consent form doesn't require revision. The protocol is attached in Section S.

Amendment Submit Date: 05/19/2017

Reason: Multiple Amendments
Description: Protocol v 2017 05 11 Randomization: Section 6, page 16 Added: Volunteers will be encouraged to washout of medication for 14 days. If they choose to remain on medicine, they will stay on same dose for duration of the study Inclusion Criteria: Section 7.1, page 16 Age limits is now 15-80. Exclusion Criteria: Section 7.2, page 18 Deleted: #6. Risk/Benefits Assessment: Section 16.1.2, page 29 Added: If side effects occur, they will be managed as effectively as possible.

Amendment Submit Date: 05/19/2017
Reason: Multiple Amendments
Description: Protocol v 2017 05 11 Randomization: Section 6, page 16 Added: Volunteers will be encouraged to washout of medication for 14 days. If they choose to remain on medicine, they will stay on same dose for duration of the study Inclusion Criteria: Section 7.1, page 16 Age limits is now 15-80. Exclusion Criteria: Section 7.2, page 18 Deleted: #6. Risk/Benefits Assessment: Section 16.1.2, page 29 Added: If side effects occur, they will be managed as effectively as possible.

Amendment Submit Date: 04/14/2017
Reason: Change/Add Procedure
Description: Protocol v. 3/15/17 1. Clarifies age of males to be PSA tested PSA age to be checked is on male patients 50 years or older, unless has a family history of prostate cancer or is of African American decent then PSA age to be checked is at age 40 years old. 2. Serum pregnancy test changed to urine pregnancy test Urine Pregnancy test (for females only). If positive, a serum pregnancy test will be conducted to confirm.

Amendment Submit Date: 09/09/2016
Reason: Other Amendment
Description: Protocol V. 8/20/2016 Study Procedures: Screening Visit: Added: OAB-Patient Satisfaction with Treatment Questionnaire (OAB-PSTQ) Added: 'twice a day' to Dispense an antibiotic Appendix I: Schedule of Events: Added OAB-PSTQ to Screening Visit Appendix V: Questionnaires: Revised OAB-PSTQ's questions 15 and 16 for clarification Revised ClinicalTrials.gov record. See Section S. The consent form has been revised to clarify the dosage of the capsules from two capsule once a day to one capsule twice a day . This was overlooked in the initial submission of this protocol.

Amendment Submit Date: 08/04/2016
Reason: Multiple Amendments
Description: Protocol v.8/1/16 1. Eligibility Criteria has been revised to allow for greater enrollment. The changes do not affect subject safety. 2. Study Procedures: - Kidney ultrasound at Screening visit is now acceptable for 1 year prior to enrollment and Visit 6 ultrasound has been deleted. - Urine biomarker testing has been removed at Visit 1. - Urodynamic procedures have been revised to meet TIRR's standard procedures. - The use of Cirpo as the antibiotic of choice has been changed to Bactrim. - Wash out period for overactivity drugs has been changed to 2 weeks prior to treatment visit. - Local anesthesia will be used in patients with sensate bladder or at risk for automatic dyreflexia. 3. Appendix I: Schedule of Events has been revised to reflect changes in study procedures. 4. Appendix II: Urine Collection and Processing Protocol has been changed to reflect William Beaumont Health System's current practice. The following documents have been added to Section S: Protocol v.8/1/16, Protocol Changes v.8/1/16, Bactrim package insert.

March 31, 2017



CHRISTOPHER PATRICK SMITH
BAYLOR COLLEGE OF MEDICINE
UROLOGY

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Email: irb@bcm.tmc.edu

H-34972 - A DOUBLE-BLIND, RANDOMIZED STUDY OF THE SAFETY AND EFFICACY OF ONABOTULINUMTOXINA (ONABONT-A) VERSUS ORAL OXYBUTYNIN IN SPINAL CORD INJURED PATIENTS WITH NEUROGENIC DETRUSOR OVERACTIVITY (PROTOCOL NUMBER 11-09-10-04) (TIRR)

APPROVAL VALID FROM 3/31/2017 TO 3/30/2018

Dear Dr. SMITH

The Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals (BCM IRB) is pleased to inform you that the research protocol and consent form(s) named above were reviewed by Full Board procedures on 3/29/2017 by Board 6 and is now approved.

The study may not continue after the approval period without additional IRB review and approval for continuation. You will receive an email renewal reminder notice prior to study expiration; however, it is your responsibility to assure that this study is not conducted beyond the expiration date.

Please be aware that only IRB-approved informed consent forms may be used when written informed consent is required.

Any changes in study or informed consent procedure must receive review and approval prior to implementation unless the change is necessary for the safety of subjects. In addition, you must inform the IRB of adverse events encountered during the study or of any new and significant information that may impact a research participants' safety or willingness to continue in your study.

The BCM IRB is organized, operates, and is registered with the United States Office for Human Research Protections according to the regulations codified in the United States Code of Federal Regulations at 45 CFR 46 and 21 CFR 56. The BCM IRB operates under the BCM Federal Wide Assurance No. 00000286, as well as those of hospitals and institutions affiliated with the College.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Flor Munoz-Rivas".

FLOR MUNOZ-RIVAS, M.D.
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals



Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

ONAbO NT-A versus Oxybutynin ER in Patients with SCI and NDO

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Background

Please read this form carefully. Take time to ask the doctor or study staff as many questions about the study as you would like. If there are any words or information that you do not understand, the doctor or study staff will explain them to you. Reading this form and talking to the doctor or study staff may help you decide whether to participate or not. If you decide to take part in the study, you must sign and date the statement of consent and authorization on the last page of this form.

Neurogenic detrusor overactivity (NDO) is a condition in which the bladder is hyperactive, often resulting in urinary incontinence (UI - not able to control urine flow). A patient who has a spinal cord injury (SCI) often suffers with NDO.

Current treatment of UI resulting from NDO includes drugs that may help with the incontinence but they are likely to cause dry mouth, constipation and blurred vision.

ONAbO NT-A [BOTOX (R)] bladder injections have been studied in other clinical research trials in patients who have not responded to oral medications. The results have shown an improvement in how often urine leakage happens and an increase in the amount of urine the bladder can hold. ONAbO NT-A is approved by the FDA for bladder injections.

Oxybutynin ER (extended release) relaxes bladder smooth muscle. In patients with UI, studies have demonstrated that Oxybutynin ER increases bladder capacity, diminishes the frequency of urine loss, and delays the initial desire to urinate. Oxybutynin ER thus decreases urgency and the frequency of both incontinent episodes and voluntary urination. Oxybutynin ER is approved by the FDA for patients with UI.

You are being asked to participate in this clinical research study because you are a patient with a spinal cord injury and have NDO.

This research study is funded by the Department of Defense

Purpose

This purpose of this clinical trial is to see if ONAbO NT-A is safe and how well it works when injected into the bladder for the treatment of UI and if it works better than oxybutynin [Ditropan (R)] that is taken by mouth. A second purpose of the study is to perform research tests on your urine samples. Urine presents a rich source of information for bladder diseases and the biomarkers (the chemical make-up of the urine cells) will be examined to learn if there are yet undiscovered reasons for urinary diseases.

OPTIONAL RESEARCH: Future research projects using your urine samples may lead to better treatment of urinary diseases.

Procedures

The research will be conducted at the following location(s):

Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research.

CPS protocol v. 8/20/16

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If you decide to be in this study, you will be asked to sign this informed consent document. You will be taking part in the study for at least 6-7 months and will visit the clinic at least 5 times.

This is a double blind study, which means that neither you nor your study doctor will know which study drugs you are receiving. However, your study doctor can get this information quickly in case of a health-related emergency.

You will be randomized to one of two treatments. The treatment you will be receiving is determined by random like the toss of a coin. You will have a 50-50 chance of receiving either treatment. The treatments are ARM 1: ONAbNT bladder injection and one placebo (sugar pills) oral medication twice a day; or ARM 2: placebo (saline or salt water) bladder injection and Oxybutynin ER (like Ditropan) one capsule twice a day.

VISIT 1 - Screening

After your informed consent is obtained, the following will occur at least 2 weeks but not more than 4 weeks prior to Visit 2: randomization and bladder injection:

1. You will have a physical examination. The study staff will ask about your medical history including the medications you are now taking and procedures you have had.
2. Your vital signs (blood pressure, temperature and pulse rate) and weight will be measured.
3. You will have a kidney ultrasound or results of exam conducted within 1 year of enrollment. An ultrasound test is a radiology technique, which uses high -frequency sound waves to produce images of the organs and structures of the body. The sound waves are sent through body tissues with a device called a transducer. The transducer is placed directly on top of the skin, which has a gel applied to the surface. The sound waves that are sent by the transducer through the body are then reflected by internal structures as "echoes." These echoes return to the transducer and are transmitted electrically onto a viewing monitor. After the ultrasound, the gel is easily wiped off.
4. You will give about 3 teaspoons of blood to test the following:
 - To see if your blood count is normal.
 - If you are a female, to confirm that you are not pregnant.
 - If you are a male, to test your PSA (Prostate specific antigen) which is a test used to screen for cancer of the prostate.
5. You will give a urine sample for routine tests.
6. You will complete the OAB-Patient Satisfaction with Treatment Questionnaire. It will take about 10 minutes for your to complete the questionnaire.
7. You will have urodynamic studies to give a baseline reading of what your bladder function is before you start the treatment. If you have had these studies within the past 12 months and you were not taking an medications for your overactive bladder, you will not need the studies at this visit. This test gives the doctors detailed information about the way your bladder and bladder outlet (the urethra) work when you try to urinate. It helps explain why you may have difficulty holding urine or urinary frequency . During this

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procedure, catheters with pressure sensors are placed through the urethra into your bladder and also into your rectum. The pressure in your bladder and rectum are measured while your bladder is filled with saline or dye solution. You will be asked questions about how full you feel and when you have the urge to urinate. You will be asked to urinate, if possible, during the study. X-rays and photos may be taken during the study.

8. If you are able to urinate, you will have a PVR (Post-Void Residual) test. The volume of fluid remaining in the bladder immediately after you urinate will be measured by catheterization (tube inserted into your bladder), or abdominal or vaginal ultrasound.

9. You will be given a bladder diary to keep track of the number of times you urinate, the amount, any leakage, etc. for 7 straight days in the week prior to next clinic visit.

10. You will be given a prescription for an antibiotic. You will take the antibiotic 3 days BEFORE your next visit, on the morning of the visit, and for 3 days AFTER the bladder injection.

11. You will be told to stop taking any medications for overactive bladder symptoms for two weeks prior to the bladder injection.

VISIT 2: Randomization and Treatment (14 days to 6 weeks after Visit 1)

The following procedures and events will happen during this visit:

1. Your vital signs and weight will be measured.
2. If you are a female, you give about 2 teaspoons of blood to confirm that you are not pregnant.
3. You will give a urine sample for routine tests and to use as a baseline for research testing.
4. If you are able to urinate, you will have a PVR.
5. The study doctor or a study staff member will review your current medications and ask about any problems you may have had since the last study visit.
6. You will confirm that you did not take any medications for your overactive bladder symptoms for the past two weeks.
7. You will complete the Incontinence Quality of Life questionnaire (I-QOL) and Incontinence Quality of Life neurogenic module (I-QOLNM) questionnaires prior to treatment. It will take about 15-20 minutes to complete the questionnaires.
8. Your bladder diary will be reviewed by the study staff. You will be given a bladder diary to keep track of the number of times you urinate, the amount, any leakage, etc. for 7 straight days in the week prior to next clinic visit.

You will be randomized into your treatment group.

After randomization, the following events will occur:

8. Your bladder injection procedure will be done according to standard procedures in the clinic. The doctor will decide if you will be given a local anesthesia to lessen the pain before beginning the injection procedure. Your bladder will be filled with saline so that the area is free of urine. The injection will be

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given. The study doctor will discuss the procedure with you. After the injection, you will be observed for at least 30 minutes before you can go home. You will be instructed to continue your antibiotics for 3 more days.

9. You will be given the study oral medication dose while at the clinic and some to take home. You are to take the study medication as one capsule twice a day every day. You will be given a diary that you will complete to help you remember to take your medication. Please bring the pill bottle and the diary with you to your next clinic visit.

10. You will complete the bladder diary for 7 consecutive days in a row prior to next clinic visit in about 2 weeks.

VISIT 3: Telephone Visit (Day 3 to 5 after injection)

You will be contacted by telephone to discuss your well-being, any changes in your medications, your antibiotic compliance, and any side-effects or adverse events you may have experienced.

VISITS 4: Week 4 after injection (plus or minus 3 days)

1. Your vital signs and weight will be measured.
2. If you are able to urinate, you will have a PVR test.
3. If you are a female, you give about 2 teaspoons of blood to confirm that you are not pregnant.
4. You will give a urine sample for routine tests and research testing.
5. Your bladder diary will be reviewed by the study staff. You will be given a bladder diary to keep track of the number of times you urinate, the amount, any leakage, etc. for 7 straight days in the week prior to next clinic visit.
6. The study doctor or a study staff member will review your medications and ask about any adverse events you may have had.
7. You will complete the I-QOL, I-QOLNM, OAB-Patient Satisfaction with Treatment Questionnaire (OAB_PSTQ), and Patient Global Assessment (PGA) questionnaires. It will take you about 20 to 30 minutes to complete them.
8. You will be given the study oral medication dose and the pill diary. Please bring the pill bottle and the diary with you to your next clinic visit.

VISIT 5: Week 12 after injection (plus or minus 3 days)

The procedures for this clinic visit are the same as VISIT 4. In addition, you will also undergo a urodynamic study as you did at Visit 1.

VISIT 6: Week 24: End of Study/Study Exit (2 weeks plus or minus 3 days after injection)

1. You will undergo a physical examination that includes your vital signs and weight measurements.
2. If you are able to urinate, you will have a PVR test.

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3. You will give a urine sample for routine tests and research testing.
4. You will give about 3 teaspoons of blood to check your general health.
5. If you are a female, your give about 2 teaspoons of blood to confirm that you are not pregnant.
6. You will give your completed bladder diary to the study doctor or staff.
7. The study doctor or a study staff member will review your medications and ask about any adverse events you may have had.
8. You will complete same 4 questionnaires as you did in VISIT 4.

This ends your participation in this research study.

If you are a male, you will have a total of approximately 6 teaspoons of blood drawn during the study. If you are a female, you will have a total of approximately 12 teaspoons of blood drawn during the study.

A portion of your urine samples will be sent to the Beaumont Research Institute at the Oakland University William Beaumont School of Medicine in Royal Oak, MI for research testing conducted under the supervision of Dr. Michael B. Chancellor. The samples will be coded so that only your study doctor will know how to link your name and other identifying information with the coded sample. The staff at the testing site will not be able to link the code to your information.

OPTIONAL RESEARCH:

With your permission, after research testing required for this study is completed, the remaining portion of your samples will be stripped of the code and will be banked for future use. It will be kept until it is all gone. Your samples will not be sold or transferred to anyone else but may be shared with the study doctor's colleagues for approved research studies. If at any time you withdraw from this study, you will not be able to get your urine samples back. You can't request that they be destroyed because the samples can't be linked to you.

Genetic testing will not be conducted on your specimens.

This institution does not plan to pay royalties to you if a commercial product is developed from blood or tissue obtained from you during this study.

You can participate in this study if you choose not to have your samples banked .

Please see next to last page of this consent form to choose your choice for this optional research.

Research related health information

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document, you give permission to people who give medical care and ensure quality from

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Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Billing or financial records

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, TIRR: The Institute for Rehabilitation and Research, and DEPARTMENT OF DEFENSE CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS and their representatives.

Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. Agents of regulatory agencies such as the U.S. Department of Health and Human Services will be permitted to inspect the research records including your health information.

The data coordinating center will have access to the research records including your health information.

A Data and Safety Monitoring Board will have access to the research records including your health information.

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law .

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research are required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that the research involves treatment. You do not have to sign this Authorization, but if you do not, you may not receive research-related treatment. To maintain the integrity of this research study,

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you generally will not have access to your personal health information related to this research until the study is complete. However, your health information that is necessary to your care will be provided to you or your physician. At the conclusion of the research and at your request, you generally will have access to your health information that Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research maintain in a designated record set, which means a set of data that includes medical information or billing records used in whole or in part by your doctors or other health care providers at Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research to make decisions about individuals. Access to your health information in a designated record set is described in the Notice of Privacy Practices provided to you by representatives of the specific institution where you are being enrolled into this research study which are: Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, DEPARTMENT OF DEFENSE CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, FDA, Baylor College of Medicine, data coordinating center, Data and Safety Monitoring Board, and TIRR: The Institute for Rehabilitation and Research may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: Christopher P. Smith, M.D.
 Scott Department of Urology
 Baylor College of Medicine
 One Baylor Plaza, BCM Stop 381,
 Houston, TX 77030

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts

ONAbNT-A: It is expected that you may have some or all of the following side effects when given ONAbNT-A. Other side effects may occur which were not seen before. Side effects are usually temporary and manageable. However, it is possible they could cause serious disease or death. The study may include risks that are unknown at this time.

There have been rare reports of serious and/or immediate or even deadly abnormally sensitive

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reactions after treatment with ONAbO NT-A. These reactions include allergic reaction, skin rash, itching, swelling, and difficulty in breathing.

It is a rare possibility that the injection of ONAbO NT-A could lead to botulism. The classic symptoms of botulism include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. The doctor's examination may reveal that the gag reflex and the deep tendon reflexes like the knee jerk are decreased or absent.

There have been rare reports of sudden death, sometimes associated with difficulty in swallowing or pneumonia. There have also been rare reports of heart problems (including irregular heartbeats and heart attack, some resulting in death). Some of these patients already had or were at risk for heart disease. It is not known if ONAbO NT-A actually caused these problems.

It should not be used when infection is present at the injection site or if you are known to be abnormally sensitive to ONAbO NT-A.

The following events have been observed since ONAbO NT-A has been marketed: skin rash, itching, and allergic reaction. In general, these side effects occur within the first week following injection and, while usually temporary, they may last several months. Pain, tenderness, or bruising around the injection site may also occur. Local weakness of the injected muscle(s) is expected. Weakness of nearby muscles may also occur due to spread of ONAbO NT-A.

ONAbO NT-A contains albumin, which comes from human blood. Although the blood is rigorously tested, there is an extremely remote risk for the transmission of viruses and similar infectious agents.

OXYBUTYNIN ER: Common Side Effects: Blurred vision; constipation; diarrhea; dizziness; drowsiness; dry eyes, nose, skin, or mouth; headache; indigestion; nausea; runny nose; stomach pain or upset; trouble sleeping; weakness

Severe Side Effects: Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); confusion; difficult or painful urination; fast or irregular heartbeat; fever; hallucinations; mental or mood changes (e.g., agitation); seizures; swelling of the hands, ankles, or feet; vision problems.

Oxybutynin ER is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin ER is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

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The concomitant use of Oxybutynin ER with other anticholinergic drugs (used to relieve cramps or spasms of the stomach, intestines, and bladder) or with other agents that produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

The safety of Oxybutynin ER administered to women who are or who may become pregnant or are breastfeeding has not been established. Therefore, Oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

LIDOCAINE(R) (given to deaden the area around the injection site): The amount of Lidocaine that you will receive usually does not cause any side effects.

Rarely, the following side effects may be experienced:

- lightheadedness
- nervousness
- anxious or scared
- feeling of well being and great happiness
- confusion
- dizziness
- drowsiness
- ringing or buzzing in the ear
- blurred or double vision
- vomiting
- sensations of heat, cold or numbness
- slight jerking motions
- shaking
- convulsions or seizures
- loss of awareness of surroundings
- difficulty breathing or not breathing at all
- slow heart beat
- low blood pressure
- stopping of the heart

Extremely rare side effects include hives, swelling, and shock.

PLACEBO: Since placebo has no active drug, your overactive bladder condition may become worse, stay the same or improve.

ANTIBIOTICS: An antibiotic may cause upset stomach, mild diarrhea, vomiting, and loss of appetite. Sensitivity to sunlight may increase. Please read the package insert that will be provided for additional

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information.

CYSTOSCOPY WITH BLADDER INJECTION: The discomfort is nearly identical to being catheterized, which generally causes slight to moderate discomfort. There will be a feeling of fullness in the bladder and a sensation to empty during the cystoscopy examination. Bleeding, infection, damage to urethra or surrounding structures may occur.

PVR: The risks of having a catheter placed in the bladder for draining the residual urine are infection of the urinary tract, injury to the urethra caused by rough insertion of the catheter, narrowing of the urethra due to scar tissue caused by the insertion of a catheter, injury to the bladder caused by incorrect insertion of the catheter.

URODYNAMICS: Generally the risks of an urodynamic study are low and are no more than those of a Foley Catheter insertion, which include the possibility of infection, trauma to the urethra or prostate, traumatic bleeding from the catheterization, discovery of previously unsuspected urethral stricture with inability to get the urodynamics catheter into the bladder.

Patients with a spinal cord injury generally occurring at the Thoracic 5 (T-5) level and above have a risk of experiencing autonomic dysreflexia during bladder filling during the urodynamic or study treatment procedures. Autonomic dysreflexia can develop suddenly, and is a possible emergency situation. Symptoms of autonomic dysreflexia include the following: elevation in blood pressure, headache, goose pimples, sweating above the level of injury, nasal congestion, slow pulse, blotching of the skin, and restlessness. If not treated promptly and correctly, it may lead to seizures, stroke, and in some cases, even death. To minimize this risk continuous blood pressure monitoring is performed throughout the study.

ULTRASOUND: Ultrasound testing is painless and harmless but the volunteer might experience anxiety in anticipation of the test. Ultrasound tests involve no radiation and studies have not revealed any adverse effects.

BLOOD DRAWS: Inserting needles into veins for collecting blood may be uncomfortable. Risks include slight bruising at the puncture site, fainting, the formation of a small blood clot or swelling of the vein and surrounding tissue, bleeding from the site, and the remote possibility of infection at the site of the needle puncture. Fainting is usually harmless, of short duration, and typically produces feelings of weakness, sweating, slowing of the heart rate and an abnormal decrease in blood pressure. Care will be taken to avoid these complications.

QUESTIONNAIRES: Completing the questionnaires may cause you to have or to experience some level of emotional discomfort due to the personal nature of the questions. The study doctor and staff will maintain a professional and caring attitude while administering the questionnaires.

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LOSS OF CONFIDENTIALITY: The loss of confidentiality regarding research information is a possibility, although, the risk is extremely small. The investigator and his staff will make every effort to maintain the confidentiality. Your urine specimens will be labeled with your subject code before being sent to Dr. Chancellor's laboratory. The laboratory personnel will not be able to know that these specimens are yours. Study documents kept at Baylor College of Medicine (BCM) may include your initials and subject code but no other identifying information. Any of your information or specimens will not contain your initials if they leave BCM.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

The benefits of participating in this study may be: improvement in urinary incontinence symptoms, decrease in the occurrence of urinary tract infections, decrease in the number of required catheterizations, and an ease of the financial burden of buying protective garments. However, you may receive no benefit from participating.

Alternatives

The following alternative procedures or treatments are available if you choose not to participate in this study: oral medications or invasive surgery to enlarge your bladder with intestine.

Subject Costs and Payments

Standard of Care: Services provided at TIRR for this disease state include clinic visits, PVRs, Kidney ultrasounds (Visits 1 and End of Study), urodynamics studies, PSA, and urinalyses. These services will be billed/paid as normally done through TIRR.

Research Costs: The events and procedures that will be paid by the study sponsor are the pregnancy tests at Visits 1, 2, 4, 5, and 6, and all study medications.

You will receive \$50 for completing each of the study visits 2, 4, 5, and 6 for a total of \$200 if all visits are completed. In order for you to receive the stipend, you will provide your name, address, telephone number, and Social Security number. You will complete the BCM Research Participant/Donor Compensation form. A check will be mailed to you.

Research Related Injury

If you experience a research related injury, please contact the Dr. Smith immediately at 713-798-4001. He will instruct you on what procedures to follow in order to receive treatment for the injury.

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Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Women of Childbearing Potential

It is possible that the medicines used in this study could injure a fetus if you or your partner becomes pregnant while taking them. Because of the potential risks involved, you or your partner should not become pregnant while you are participating in this study.

If you are sexually active or become sexually active and can get pregnant or can get your partner pregnant, you must agree to use one of the following forms of birth control every time you have sex:

- * oral contraceptives ("the pill"),
- * intrauterine devices (IUDs),
- * contraceptive implants under the skin, or contraceptive injections,
- * condoms with foam.

Should you become pregnant while on this study, you must immediately notify the study personnel.

The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can choose not to provide this information.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, CHRISTOPHER PATRICK SMITH, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: CHRISTOPHER PATRICK SMITH at 713--798-4001 24 hours a day.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office

CONSENT FORM

HIPAA Compliant

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number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

SAMPLE STORAGE: You are being asked to agree to allow samples of your urine samples which will be stored as described in the Procedures section of this informed consent document, to be used for current research use. You are also being asked to agree to allow the use of stored materials for future research use. Complete confidentiality will be maintained and these samples will not be tracked back to you, except by using records available only to the Principal Investigators, the Co-Investigators, and your urologist.

PLEASE CIRCLE YOUR CHOICES AND INITIAL:

Samples used for current research: YES NO INITIALS

Samples used for future research: YES NO INITIALS

A description of this clinical trial (NCT010504114) will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject Date

Investigator or Designee Obtaining Consent Date

Witness (if applicable) Date

Translator (if applicable) Date



Baylor College of Medicine
Office of Research
One Baylor Plaza, 600D
Houston, Texas 77030
Phone : (713) 798-6970
Fax: (713) 798-6990
Email: irb@bcm.tmc.edu

MEMORANDUM

TO: CHRISTOPHER PATRICK SMITH
UROLOGY

A handwritten signature in black ink that reads "Julia A. Thompson". The signature is written in a cursive style and is positioned above a horizontal line.

FROM: JULIA ANN THOMPSON,
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

DATE: April 14, 2017

RE: **H-34972 - A DOUBLE-BLIND, RANDOMIZED STUDY OF THE SAFETY AND EFFICACY OF ONABOTULINUMTOXINA (ONABONT-A) VERSUS ORAL OXYBUTYNIN IN SPINAL CORD INJURED PATIENTS WITH NEUROGENIC DETRUSOR OVERACTIVITY (PROTOCOL NUMBER 11-09-10-04) (TIRR)**

Your amendment, detailed below, was reviewed by Expedited procedures on April 14, 2017 by Board 6 and is now approved.

NOTE: Approved advertisement(s) should only be posted at the institution(s) where the research is being performed including approved recruitment site(s).

This is not applicable to the following advertisement modes: billboards, radio, television, internet, or website.

Description:

Protocol v. 3/15/17

1. Clarifies age of males to be PSA tested

PSA age to be checked is on male patients 50 years or older, unless has a family history of prostate cancer or is of African American decent then PSA age to be checked is at age 40 years old.

2. Serum pregnancy test changed to urine pregnancy test

Urine Pregnancy test (for females only). If positive, a serum pregnancy test will be conducted to confirm.

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Background

Please read this form carefully. Take time to ask the doctor or study staff as many questions about the study as you would like. If there are any words or information that you do not understand, the doctor or study staff will explain them to you. Reading this form and talking to the doctor or study staff may help you decide whether to participate or not. If you decide to take part in the study, you must sign and date the statement of consent and authorization on the last page of this form.

Neurogenic detrusor overactivity (NDO) is a condition in which the bladder is hyperactive, often resulting in urinary incontinence (UI - not able to control urine flow). A patient who has a spinal cord injury (SCI) often suffers with NDO.

Current treatment of UI resulting from NDO includes drugs that may help with the incontinence but they are likely to cause dry mouth, constipation and blurred vision.

ONAbO NT-A [BOTOX (R)] bladder injections have been studied in other clinical research trials in patients who have not responded to oral medications. The results have shown an improvement in how often urine leakage happens and an increase in the amount of urine the bladder can hold. ONAbO NT-A is approved by the FDA for bladder injections.

Oxybutynin ER (extended release) relaxes bladder smooth muscle. In patients with UI, studies have demonstrated that Oxybutynin ER increases bladder capacity, diminishes the frequency of urine loss, and delays the initial desire to urinate. Oxybutynin ER thus decreases urgency and the frequency of both incontinent episodes and voluntary urination. Oxybutynin ER is approved by the FDA for patients with UI.

You are being asked to participate in this clinical research study because you are a patient with a spinal cord injury and have NDO.

This research study is funded by the Department of Defense

Purpose

This purpose of this clinical trial is to see if ONAbO NT-A is safe and how well it works when injected into the bladder for the treatment of UI and if it works better than oxybutynin [Ditropan (R)] that is taken by mouth. A second purpose of the study is to perform research tests on your urine samples. Urine presents a rich source of information for bladder diseases and the biomarkers (the chemical make-up of the urine cells) will be examined to learn if there are yet undiscovered reasons for urinary diseases.

OPTIONAL RESEARCH: Future research projects using your urine samples may lead to better treatment of urinary diseases.

Procedures

The research will be conducted at the following location(s):

Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research.

CPS protocol v. 3/15/17

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If you decide to be in this study, you will be asked to sign this informed consent document. You will be taking part in the study for at least 6-7 months and will visit the clinic at least 5 times.

This is a double blind study, which means that neither you nor your study doctor will know which study drugs you are receiving. However, your study doctor can get this information quickly in case of a health-related emergency.

You will be randomized to one of two treatments. The treatment you will be receiving is determined by random like the toss of a coin. You will have a 50-50 chance of receiving either treatment. The treatments are ARM 1: ONAbNT bladder injection and one placebo (sugar pills) oral medication twice a day; or ARM 2: placebo (saline or salt water) bladder injection and Oxybutynin ER (like Ditropan) one capsule twice a day.

VISIT 1 - Screening

After your informed consent is obtained, the following will occur at least 2 weeks but not more than 4 weeks prior to Visit 2: randomization and bladder injection:

1. You will have a physical examination. The study staff will ask about your medical history including the medications you are now taking and procedures you have had.
2. Your vital signs (blood pressure, temperature and pulse rate) and weight will be measured.
3. You will have a kidney ultrasound or results of exam conducted within 1 year of enrollment. An ultrasound test is a radiology technique, which uses high -frequency sound waves to produce images of the organs and structures of the body. The sound waves are sent through body tissues with a device called a transducer. The transducer is placed directly on top of the skin, which has a gel applied to the surface. The sound waves that are sent by the transducer through the body are then reflected by internal structures as "echoes." These echoes return to the transducer and are transmitted electrically onto a viewing monitor. After the ultrasound, the gel is easily wiped off.
4. You will give about 3 teaspoons of blood to test the following:
 - To see if your blood count is normal.
 - If you are a female, to confirm that you are not pregnant.
 - Your PSA (Prostate specific antigen) which is a test used to screen for cancer of the prostate will be check if you are 50 years of age or older unless you have a family history or prostate cancer, or if you are of African American decent.. If so, the PSA will be checked if you are age 40 or older.
5. You will give a urine sample for routine tests.
6. You will complete the OAB-Patient Satisfaction with Treatment Questionnaire. It will take about 10 minutes for your to complete the questionnaire.
- 7 You will have urodynamic studies to give a baseline reading of what your bladder function is before you start the treatment. If you have had these studies within the past 12 months and you were not taking an medications for your overactive bladder, you will not need the studies at this visit. This test gives the doctors detailed information about the way your bladder and bladder outlet (the urethra) work when you

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try to urinate. It helps explain why you may have difficulty holding urine or urinary frequency. During this procedure, catheters with pressure sensors are placed through the urethra into your bladder and also into your rectum. The pressure in your bladder and rectum are measured while your bladder is filled with saline or dye solution. You will be asked questions about how full you feel and when you have the urge to urinate. You will be asked to urinate, if possible, during the study. X-rays and photos may be taken during the study.

8. If you are able to urinate, you will have a PVR (Post-Void Residual) test. The volume of fluid remaining in the bladder immediately after you urinate will be measured by catheterization (tube inserted into your bladder), or abdominal or vaginal ultrasound.

9. You will be given a bladder diary to keep track of the number of times you urinate, the amount, any leakage, etc. for 7 straight days in the week prior to next clinic visit.

10. You will be given a prescription for an antibiotic. You will take the antibiotic 3 days BEFORE your next visit, on the morning of the visit, and for 3 days AFTER the bladder injection.

11. You will be told to stop taking any medications for overactive bladder symptoms for two weeks prior to the bladder injection.

VISIT 2: Randomization and Treatment (14 days to 6 weeks after Visit 1)

The following procedures and events will happen during this visit:

1. Your vital signs and weight will be measured.
2. If you are a female, you will provide a urine specimen to check for pregnancy. If the urine test is positive, you will give about 2 teaspoons of blood to check for pregnancy.
3. You will give a urine sample for routine tests and to use as a baseline for research testing.
4. If you are able to urinate, you will have a PVR.
5. The study doctor or a study staff member will review your current medications and ask about any problems you may have had since the last study visit.
6. You will confirm that you did not take any medications for your overactive bladder symptoms for the past two weeks.
7. You will complete the Incontinence Quality of Life questionnaire (I-QOL) and Incontinence Quality of Life neurogenic module (I-QOLNM) questionnaires prior to treatment. It will take about 15-20 minutes to complete the questionnaires.
8. Your bladder diary will be reviewed by the study staff. You will be given a bladder diary to keep track of the number of times you urinate, the amount, any leakage, etc. for 7 straight days in the week prior to next clinic visit.

You will be randomized into your treatment group.

After randomization, the following events will occur:

8. Your bladder injection procedure will be done according to standard procedures in the clinic. The

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doctor will decide if you will be given a local anesthesia to lessen the pain before beginning the injection procedure. Your bladder will be filled with saline so that the area is free of urine. The injection will be given. The study doctor will discuss the procedure with you. After the injection, you will be observed for at least 30 minutes before you can go home. You will be instructed to continue your antibiotics for 3 more days.

9. You will be given the study oral medication dose while at the clinic and some to take home. You are to take the study medication as one capsule twice a day every day. You will be given a diary that you will complete to help you remember to take your medication. Please bring the pill bottle and the diary with you to your next clinic visit.

10. You will complete the bladder diary for 7 consecutive days in a row prior to next clinic visit in about 2 weeks.

VISIT 3: Telephone Visit (Day 3 to 5 after injection)

You will be contacted by telephone to discuss your well-being, any changes in your medications, your antibiotic compliance, and any side-effects or adverse events you may have experienced.

VISITS 4: Week 4 after injection (plus or minus 3 days)

1. Your vital signs and weight will be measured.
2. If you are able to urinate, you will have a PVR test.
3. If you are a female, you will provide a urine specimen to check for pregnancy. If the urine test is positive, you will give about 2 teaspoons of blood to check for pregnancy.
4. You will give a urine sample for routine tests and research testing.
5. Your bladder diary will be reviewed by the study staff. You will be given a bladder diary to keep track of the number of times you urinate, the amount, any leakage, etc. for 7 straight days in the week prior to next clinic visit.
6. The study doctor or a study staff member will review your medications and ask about any adverse events you may have had.
7. You will complete the I-QOL, I-QOLNM, OAB-Patient Satisfaction with Treatment Questionnaire (OAB_PSTQ), and Patient Global Assessment (PGA) questionnaires. It will take you about 20 to 30 minutes to complete them.
8. You will be given the study oral medication dose and the pill diary. Please bring the pill bottle and the diary with you to your next clinic visit.

VISIT 5: Week 12 after injection (plus or minus 3 days)

The procedures for this clinic visit are the same as VISIT 4. In addition, you will also undergo a urodynamic study as you did at Visit 1.

VISIT 6: Week 24: End of Study/Study Exit (2 weeks plus or minus 3 days after injection)

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1. You will undergo a physical examination that includes your vital signs and weight measurements .
2. If you are able to urinate, you will have a PVR test.
3. You will give a urine sample for routine tests and research testing .
4. You will give about 3 teaspoons of blood to check your general health.
5. If you are a female, you will give about 2 teaspoons of blood to check for pregnancy.
6. You will give your completed bladder diary to the study doctor or staff .
7. The study doctor or a study staff member will review your medications and ask about any adverse events you may have had.
8. You will complete same 4 questionnaires as you did in VISIT 4.

This ends your participation in this research study.

If you are a male, you will have a total of approximately 6 teaspoons of blood drawn during the study. If you are a female, you will have a total of approximately 12 teaspoons of blood drawn during the study.

A portion of your urine samples will be sent to the Beaumont Research Institute at the Oakland University William Beaumont School of Medicine in Royal Oak, MI for research testing conducted under the supervision of Dr. Michael B. Chancellor. The samples will be coded so that only your study doctor will know how to link your name and other identifying information with the coded sample. The staff at the testing site will not be able to link the code to your information.

OPTIONAL RESEARCH:

With your permission, after research testing required for this study is completed, the remaining portion of your samples will be stripped of the code and will be banked for future use. It will be kept until it is all gone. Your samples will not be sold or transferred to anyone else but may be shared with the study doctor's colleagues for approved research studies. If at any time you withdraw from this study, you will not be able to get your urine samples back. You can't request that they be destroyed because the samples can't be linked to you.

Genetic testing will not be conducted on your specimens.

This institution does not plan to pay royalties to you if a commercial product is developed from blood or tissue obtained from you during this study.

You can participate in this study if you choose not to have your samples banked .

Please see next to last page of this consent form to choose your choice for this optional research.

Research related health information

CPS protocol v. 3/15/17

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

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H-34972- A DOUBLE-BLIND, RANDOMIZED STUDY OF THE SAFETY AND EFFICACY OF ONABOTULINUMTOXINA (ONABONT-A) VERSUS ORAL OXYBUTYNIN IN SPINAL CORD INJURED PATIENTS WITH NEUROGENIC DETRUSOR OVERACTIVITY (PROTOCOL NUMBER 11-09-10-04) (TIRR)

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document, you give permission to people who give medical care and ensure quality from Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Billing or financial records

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, TIRR: The Institute for Rehabilitation and Research, and DEPARTMENT OF DEFENSE CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS and their representatives.

Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. Agents of regulatory agencies such as the U.S. Department of Health and Human Services will be permitted to inspect the research records including your health information.

The data coordinating center will have access to the research records including your health information.

A Data and Safety Monitoring Board will have access to the research records including your health information.

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law .

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research are required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

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Please note that the research involves treatment. You do not have to sign this Authorization, but if you do not, you may not receive research-related treatment. To maintain the integrity of this research study, you generally will not have access to your personal health information related to this research until the study is complete. However, your health information that is necessary to your care will be provided to you or your physician. At the conclusion of the research and at your request, you generally will have access to your health information that Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research maintain in a designated record set, which means a set of data that includes medical information or billing records used in whole or in part by your doctors or other health care providers at Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research to make decisions about individuals. Access to your health information in a designated record set is described in the Notice of Privacy Practices provided to you by representatives of the specific institution where you are being enrolled into this research study which are: Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, DEPARTMENT OF DEFENSE CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, FDA, Baylor College of Medicine, data coordinating center, Data and Safety Monitoring Board, and TIRR: The Institute for Rehabilitation and Research may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: Christopher P. Smith, M.D.
 Scott Department of Urology
 Baylor College of Medicine
 One Baylor Plaza, BCM Stop 381,
 Houston, TX 77030

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts

ONAbNT-A: It is expected that you may have some or all of the following side effects when given ONAbNT-A. Other side effects may occur which were not seen before. Side effects are usually temporary and manageable. However, it is possible they could cause serious disease or death. The

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study may include risks that are unknown at this time.

There have been rare reports of serious and/or immediate or even deadly abnormally sensitive reactions after treatment with ONAbO NT-A. These reactions include allergic reaction, skin rash, itching, swelling, and difficulty in breathing.

It is a rare possibility that the injection of ONAbO NT-A could lead to botulism. The classic symptoms of botulism include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. The doctor's examination may reveal that the gag reflex and the deep tendon reflexes like the knee jerk are decreased or absent.

There have been rare reports of sudden death, sometimes associated with difficulty in swallowing or pneumonia. There have also been rare reports of heart problems (including irregular heartbeats and heart attack, some resulting in death). Some of these patients already had or were at risk for heart disease. It is not known if ONAbO NT-A actually caused these problems.

It should not be used when infection is present at the injection site or if you are known to be abnormally sensitive to ONAbO NT-A.

The following events have been observed since ONAbO NT-A has been marketed: skin rash, itching, and allergic reaction. In general, these side effects occur within the first week following injection and, while usually temporary, they may last several months. Pain, tenderness, or bruising around the injection site may also occur. Local weakness of the injected muscle(s) is expected. Weakness of nearby muscles may also occur due to spread of ONAbO NT-A.

ONAbO NT-A contains albumin, which comes from human blood. Although the blood is rigorously tested, there is an extremely remote risk for the transmission of viruses and similar infectious agents.

OXYBUTYNIN ER: Common Side Effects: Blurred vision; constipation; diarrhea; dizziness; drowsiness; dry eyes, nose, skin, or mouth; headache; indigestion; nausea; runny nose; stomach pain or upset; trouble sleeping; weakness

Severe Side Effects: Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); confusion; difficult or painful urination; fast or irregular heartbeat; fever; hallucinations; mental or mood changes (e.g., agitation); seizures; swelling of the hands, ankles, or feet; vision problems.

Oxybutynin ER is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

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Oxybutynin ER is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

The concomitant use of Oxybutynin ER with other anticholinergic drugs (used to relieve cramps or spasms of the stomach, intestines, and bladder) or with other agents that produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

The safety of Oxybutynin ER administered to women who are or who may become pregnant or are breastfeeding has not been established. Therefore, Oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

LIDOCAINE(R) (given to deaden the area around the injection site): The amount of Lidocaine that you will receive usually does not cause any side effects.

Rarely, the following side effects may be experienced:

- lightheadedness
- nervousness
- anxious or scared
- feeling of well being and great happiness
- confusion
- dizziness
- drowsiness
- ringing or buzzing in the ear
- blurred or double vision
- vomiting
- sensations of heat, cold or numbness
- slight jerking motions
- shaking
- convulsions or seizures
- loss of awareness of surroundings
- difficulty breathing or not breathing at all
- slow heart beat
- low blood pressure
- stopping of the heart

Extremely rare side effects include hives, swelling, and shock.

PLACEBO: Since placebo has no active drug, your overactive bladder condition may become worse, stay the same or improve.

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ANTIBIOTICS: An antibiotic may cause upset stomach, mild diarrhea, vomiting, and loss of appetite. Sensitivity to sunlight may increase. Please read the package insert that will be provided for additional information.

CYSTOSCOPY WITH BLADDER INJECTION: The discomfort is nearly identical to being catheterized, which generally causes slight to moderate discomfort. There will be a feeling of fullness in the bladder and a sensation to empty during the cystoscopy examination. Bleeding, infection, damage to urethra or surrounding structures may occur.

PVR: The risks of having a catheter placed in the bladder for draining the residual urine are infection of the urinary tract, injury to the urethra caused by rough insertion of the catheter, narrowing of the urethra due to scar tissue caused by the insertion of a catheter, injury to the bladder caused by incorrect insertion of the catheter.

URODYNAMICS: Generally the risks of an urodynamic study are low and are no more than those of a Foley Catheter insertion, which include the possibility of infection, trauma to the urethra or prostate, traumatic bleeding from the catheterization, discovery of previously unsuspected urethral stricture with inability to get the urodynamics catheter into the bladder.

Patients with a spinal cord injury generally occurring at the Thoracic 5 (T-5) level and above have a risk of experiencing autonomic dysreflexia during bladder filling during the urodynamic or study treatment procedures. Autonomic dysreflexia can develop suddenly, and is a possible emergency situation. Symptoms of autonomic dysreflexia include the following: elevation in blood pressure, headache, goose pimples, sweating above the level of injury, nasal congestion, slow pulse, blotching of the skin, and restlessness. If not treated promptly and correctly, it may lead to seizures, stroke, and in some cases, even death. To minimize this risk continuous blood pressure monitoring is performed throughout the study.

ULTRASOUND: Ultrasound testing is painless and harmless but the volunteer might experience anxiety in anticipation of the test. Ultrasound tests involve no radiation and studies have not revealed any adverse effects.

BLOOD DRAWS: Inserting needles into veins for collecting blood may be uncomfortable. Risks include slight bruising at the puncture site, fainting, the formation of a small blood clot or swelling of the vein and surrounding tissue, bleeding from the site, and the remote possibility of infection at the site of the needle puncture. Fainting is usually harmless, of short duration, and typically produces feelings of weakness, sweating, slowing of the heart rate and an abnormal decrease in blood pressure. Care will be taken to avoid these complications.

QUESTIONNAIRES: Completing the questionnaires may cause you to have or to experience some

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level of emotional discomfort due to the personal nature of the questions. The study doctor and staff will maintain a professional and caring attitude while administering the questionnaires.

LOSS OF CONFIDENTIALITY: The loss of confidentiality regarding research information is a possibility, although, the risk is extremely small. The investigator and his staff will make every effort to maintain the confidentiality. Your urine specimens will be labeled with your subject code before being sent to Dr. Chancellor's laboratory. The laboratory personnel will not be able to know that these specimens are yours. Study documents kept at Baylor College of Medicine (BCM) may include your initials and subject code but no other identifying information. Any of your information or specimens will not contain your initials if they leave BCM.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

The benefits of participating in this study may be: improvement in urinary incontinence symptoms, decrease in the occurrence of urinary tract infections, decrease in the number of required catheterizations, and an ease of the financial burden of buying protective garments. However, you may receive no benefit from participating.

Alternatives

The following alternative procedures or treatments are available if you choose not to participate in this study: oral medications or invasive surgery to enlarge your bladder with intestine.

Subject Costs and Payments

Standard of Care: Services provided at TIRR for this disease state include clinic visits, PVRs, Kidney ultrasounds (Visits 1 and End of Study), urodynamics studies, PSA, and urinalyses. These services will be billed/paid as normally done through TIRR.

Research Costs: The events and procedures that will be paid by the study sponsor are the pregnancy tests at Visits 1, 2, 4, 5, and 6, and all study medications.

You will receive \$50 for completing each of the study visits 2, 4, 5, and 6 for a total of \$200 if all visits are completed. In order for you to receive the stipend, you will provide your name, address, telephone number, and Social Security number. You will complete the BCM Research Participant/Donor Compensation form. A check will be mailed to you.

Research Related Injury

If you experience a research related injury, please contact the Dr. Smith immediately at 713-798-4001. He will instruct you on what procedures to follow in order to receive treatment for the injury.

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Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Women of Childbearing Potential

It is possible that the medicines used in this study could injure a fetus if you or your partner becomes pregnant while taking them. Because of the potential risks involved, you or your partner should not become pregnant while you are participating in this study.

If you are sexually active or become sexually active and can get pregnant or can get your partner pregnant, you must agree to use one of the following forms of birth control every time you have sex:

- * oral contraceptives ("the pill"),
- * intrauterine devices (IUDs),
- * contraceptive implants under the skin, or contraceptive injections,
- * condoms with foam.

Should you become pregnant while on this study, you must immediately notify the study personnel.

The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can choose not to provide this information.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, CHRISTOPHER PATRICK SMITH, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: CHRISTOPHER PATRICK SMITH at 713--798-4001 24 hours a day.

CONSENT FORM

HIPAA Compliant

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Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

SAMPLE STORAGE: You are being asked to agree to allow samples of your urine samples which will be stored as described in the Procedures section of this informed consent document, to be used for current research use. You are also being asked to agree to allow the use of stored materials for future research use. Complete confidentiality will be maintained and these samples will not be tracked back to you, except by using records available only to the Principal Investigators, the Co-Investigators, and your urologist.

PLEASE CIRCLE YOUR CHOICES AND INITIAL:

Samples used for current research: YES NO INITIALS

Samples used for future research: YES NO INITIALS

A description of this clinical trial (NCT010504114) will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

CONSENT FORM

HIPAA Compliant

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject Date

Investigator or Designee Obtaining Consent Date

Witness (if applicable) Date

Translator (if applicable) Date



Baylor College of Medicine
Office of Research
One Baylor Plaza, 600D
Houston, Texas 77030
Phone : (713) 798-6970
Fax: (713) 798-6990
Email: irb@bcm.tmc.edu

MEMORANDUM

TO: CHRISTOPHER PATRICK SMITH
UROLOGY

FROM: JULIE PAMELA KATKIN, M.D. 
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

DATE: June 19, 2017

RE: **H-34972 - A DOUBLE-BLIND, RANDOMIZED STUDY OF THE SAFETY AND EFFICACY OF ONABOTULINUMTOXINA (ONABONT-A) VERSUS ORAL OXYBUTYNIN IN SPINAL CORD INJURED PATIENTS WITH NEUROGENIC DETRUSOR OVERACTIVITY (PROTOCOL NUMBER 11-09-10-04) (TIRR)**

Your amendment, detailed below, was reviewed by Full Board procedures on 6/7/2017 by Board 2 and is now approved.

NOTE: Approved advertisement(s) should only be posted at the institution(s) where the research is being performed including approved recruitment site(s).

This is not applicable to the following advertisement modes: billboards, radio, television, internet, or website.

Description:

Protocol v 2017 05 11

Randomization: Section 6, page 16

Added: Volunteers will be encouraged to washout of medication for 14 days. If they choose to remain on medicine, they will stay on same dose for duration of the study

Inclusion Criteria: Section 7.1, page 16

Age limits is now 15-80.

Exclusion Criteria: Section 7.2, page 18

Deleted: #6.

Risk/Benefits Assessment: Section 16.1.2, page 29

Added: If side effects occur, they will be managed as effectively as possible.

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Background

Please read this form carefully. In this consent form, "you" refers to you or your child.

Take time to ask the doctor or study staff as many questions about the study as you would like. If there are any words or information that you do not understand, the doctor or study staff will explain them to you. Reading this form and talking to the doctor or study staff may help you decide whether to participate or not. If you decide to take part in the study, you must sign and date the statement of consent and authorization on the last page of this form.

Neurogenic detrusor overactivity (NDO) is a condition in which the bladder is hyperactive, often resulting in urinary incontinence (UI - not able to control urine flow). A patient who has a spinal cord injury (SCI) often suffers with NDO.

Current treatment of UI resulting from NDO includes drugs that may help with the incontinence but they are likely to cause dry mouth, constipation and blurred vision.

ONAbO NT-A [BOTOX (R)] bladder injections have been studied in other clinical research trials in patients who have not responded to oral medications. The results have shown an improvement in how often urine leakage happens and an increase in the amount of urine the bladder can hold. ONAbO NT-A is approved by the FDA for bladder injections.

Oxybutynin ER (extended release) relaxes bladder smooth muscle. In patients with UI, studies have demonstrated that Oxybutynin ER increases bladder capacity, diminishes the frequency of urine loss, and delays the initial desire to urinate. Oxybutynin ER thus decreases urgency and the frequency of both incontinent episodes and voluntary urination. Oxybutynin ER is approved by the FDA for patients with UI.

You are being asked to participate in this clinical research study because you are a patient with a spinal cord injury and have NDO.

This research study is funded by the Department of Defense

Purpose

This purpose of this clinical trial is to see if ONAbO NT-A is safe and how well it works when injected into the bladder for the treatment of UI and if it works better than oxybutynin [Ditropan (R)] that is taken by mouth. A second purpose of the study is to perform research tests on your urine samples. Urine presents a rich source of information for bladder diseases and the biomarkers (the chemical make-up of the urine cells) will be examined to learn if there are yet undiscovered reasons for urinary diseases.

OPTIONAL RESEARCH: Future research projects using your urine samples may lead to better treatment of urinary diseases.

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Procedures

The research will be conducted at the following location(s):

Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research.

If you decide to be in this study, you will be asked to sign this informed consent document. You will be taking part in the study for at least 6-7 months and will visit the clinic at least 5 times.

This is a double blind study, which means that neither you nor your study doctor will know which study drugs you are receiving. However, your study doctor can get this information quickly in case of a health-related emergency.

You will be randomized to one of two treatments. The treatment you will be receiving is determined by random like the toss of a coin. You will have a 50-50 chance of receiving either treatment. The treatments are ARM 1: ONAbO NT bladder injection and one placebo (sugar pills) oral medication twice a day; or ARM 2: placebo (saline or salt water) bladder injection and Oxybutynin ER (like Ditropan) one capsule twice a day.

VISIT 1 - Screening

After your informed consent is obtained, the following will occur at least 2 weeks but not more than 4 weeks prior to Visit 2: randomization and bladder injection:

1. You will have a physical examination. The study staff will ask about your medical history including the medications you are now taking and procedures you have had.
2. Your vital signs (blood pressure, temperature and pulse rate) and weight will be measured.
3. You will have a kidney ultrasound or results of exam conducted within 1 year of enrollment. An ultrasound test is a radiology technique, which uses high -frequency sound waves to produce images of the organs and structures of the body. The sound waves are sent through body tissues with a device called a transducer. The transducer is placed directly on top of the skin, which has a gel applied to the surface. The sound waves that are sent by the transducer through the body are then reflected by internal structures as "echoes." These echoes return to the transducer and are transmitted electrically onto a viewing monitor. After the ultrasound, the gel is easily wiped off.
4. You will give about 3 teaspoons of blood to test the following:
 - To see if your blood count is normal.
 - If you are a female, to confirm that you are not pregnant.
 - Your PSA (Prostate specific antigen) which is a test used to screen for cancer of the prostate will be check if you are 50 years of age or older unless you have a family history or prostate cancer, or if you are of African American decent.. If so, the PSA will be checked if you are age 40 or older.
5. You will give a urine sample for routine tests.
6. You will complete the OAB-Patient Satisfaction with Treatment Questionnaire. It will take about 10 minutes for your to complete the questionnaire.
- 7 You will have urodynamic studies to give a baseline reading of what your bladder function is before

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you start the treatment. If you have had these studies within the past 12 months and you were not taking an medications for your overactive bladder, you will not need the studies at this visit. This test gives the doctors detailed information about the way your bladder and bladder outlet (the urethra) work when you try to urinate. It helps explain why you may have difficulty holding urine or urinary frequency . During this procedure, catheters with pressure sensors are placed through the urethra into your bladder and also into your rectum. The pressure in your bladder and rectum are measured while your bladder is filled with saline or dye solution. You will be asked questions about how full you feel and when you have the urge to urinate. You will be asked to urinate, if possible, during the study. X-rays and photos may be taken during the study.

8. If you are able to urinate, you will have a PVR (Post-Void Residual) test. The volume of fluid remaining in the bladder immediately after you urinate will be measured by catheterization (tube inserted into your bladder), or abdominal or vaginal ultrasound.

9. You will be given a bladder diary to keep track of the number of times you urinate , the amount, any leakage, etc. for 7 straight days in the week prior to next clinic visit.

10. You will be given a prescription for an antibiotic. You will take the antibiotic 3 days BEFORE your next visit, on the morning of the visit, and for 3 days AFTER the bladder injection.

11. You will be encouraged to stop taking any medications for overactive bladder symptoms for two weeks prior to the bladder injection.

VISIT 2: Randomization and Treatment (14 days to 6 weeks after Visit 1)

The following procedures and events will happen during this visit:

1. Your vital signs and weight will be measured.
2. If you are a female, you will provide a urine specimen to check for pregnancy. If the urine test is positive, you will give about 2 teaspoons of blood to check for pregnancy.
3. You will give a urine sample for routine tests and to use as a baseline for research testing .
4. If you are able to urinate, you will have a PVR.
5. The study doctor or a study staff member will review your current medications and ask about any problems you may have had since the last study visit.
6. You will be asked if you took any medications for your overactive bladder symptoms for the past two weeks.
7. You will complete the Incontinence Quality of Life questionnaire (I-QOL) and Incontinence Quality of Life neurogenic module (I-QOLNM) questionnaires prior to treatment. It will take about 15-20 minutes to complete the questionnaires.
8. Your bladder diary will be reviewed by the study staff. You will be given a bladder diary to keep track of the number of times you urinate, the amount, any leakage, etc. for 7 straight days in the week prior to next clinic visit.

You will be randomized into your treatment group.

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After randomization, the following events will occur:

8. Your bladder injection procedure will be done according to standard procedures in the clinic. The doctor will decide if you will be given a local anesthesia to lessen the pain before beginning the injection procedure. Your bladder will be filled with saline so that the area is free of urine. The injection will be given. The study doctor will discuss the procedure with you. After the injection, you will be observed for at least 30 minutes before you can go home. You will be instructed to continue your antibiotics for 3 more days.
9. You will be given the study oral medication dose while at the clinic and some to take home. You are to take the study medication as one capsule twice a day every day. You will be given a diary that you will complete to help you remember to take your medication. Please bring the pill bottle and the diary with you to your next clinic visit.
10. You will complete the bladder diary for 7 consecutive days in a row prior to next clinic visit in about 2 weeks.

VISIT 3: Telephone Visit (Day 3 to 5 after injection)

You will be contacted by telephone to discuss your well-being, any changes in your medications, your antibiotic compliance, and any side-effects or adverse events you may have experienced.

VISITS 4: Week 4 after injection (plus or minus 3 days)

1. Your vital signs and weight will be measured.
2. If you are able to urinate, you will have a PVR test.
3. If you are a female, you will provide a urine specimen to check for pregnancy. If the urine test is positive, you will give about 2 teaspoons of blood to check for pregnancy.
4. You will give a urine sample for routine tests and research testing.
5. Your bladder diary will be reviewed by the study staff. You will be given a bladder diary to keep track of the number of times you urinate, the amount, any leakage, etc. for 7 straight days in the week prior to next clinic visit.
6. The study doctor or a study staff member will review your medications and ask about any adverse events you may have had.
7. You will complete the I-QOL, I-QOLNM, OAB-Patient Satisfaction with Treatment Questionnaire (OAB_PSTQ), and Patient Global Assessment (PGA) questionnaires. It will take you about 20 to 30 minutes to complete them.
8. You will be given the study oral medication dose and the pill diary. Please bring the pill bottle and the diary with you to your next clinic visit.

VISIT 5: Week 12 after injection (plus or minus 3 days)

The procedures for this clinic visit are the same as VISIT 4. In addition, you will also undergo a

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urodynamic study as you did at Visit 1.

VISIT 6: Week 24: End of Study/Study Exit (2 weeks plus or minus 3 days after injection)

1. You will undergo a physical examination that includes your vital signs and weight measurements .
2. If you are able to urinate, you will have a PVR test.
3. You will give a urine sample for routine tests and research testing.
4. You will give about 3 teaspoons of blood to check your general health.
5. If you are a female, you will give about 2 teaspoons of blood to check for pregnancy.
6. You will give your completed bladder diary to the study doctor or staff.
7. The study doctor or a study staff member will review your medications and ask about any adverse events you may have had.
8. You will complete same 4 questionnaires as you did in VISIT 4.

This ends your participation in this research study.

If you are a male, you will have a total of approximately 6 teaspoons of blood drawn during the study. If you are a female, you will have a total of approximately 12 teaspoons of blood drawn during the study.

A portion of your urine samples will be sent to the Beaumont Research Institute at the Oakland University William Beaumont School of Medicine in Royal Oak, MI for research testing conducted under the supervision of Dr. Michael B. Chancellor. The samples will be coded so that only your study doctor will know how to link your name and other identifying information with the coded sample. The staff at the testing site will not be able to link the code to your information.

OPTIONAL RESEARCH:

With your permission, after research testing required for this study is completed, the remaining portion of your samples will be stripped of the code and will be banked for future use. It will be kept until it is all gone. Your samples will not be sold or transferred to anyone else but may be shared with the study doctor's colleagues for approved research studies. If at any time you withdraw from this study, you will not be able to get your urine samples back. You can't request that they be destroyed because the samples can't be linked to you.

Genetic testing will not be conducted on your specimens.

This institution does not plan to pay royalties to you if a commercial product is developed from blood or tissue obtained from you during this study.

You can participate in this study if you choose not to have your samples banked .

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Please see next to last page of this consent form to choose your choice for this optional research.

Research related health information

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document, you give permission to people who give medical care and ensure quality from Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Billing or financial records

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, TIRR: The Institute for Rehabilitation and Research, and DEPARTMENT OF DEFENSE CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS and their representatives.

Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. Agents of regulatory agencies such as the U.S. Department of Health and Human Services will be permitted to inspect the research records including your health information.

The data coordinating center will have access to the research records including your health information.

A Data and Safety Monitoring Board will have access to the research records including your health information.

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law .

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research are required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research to use and/or disclose (release) your health

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information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that the research involves treatment. You do not have to sign this Authorization, but if you do not, you may not receive research-related treatment. To maintain the integrity of this research study, you generally will not have access to your personal health information related to this research until the study is complete. However, your health information that is necessary to your care will be provided to you or your physician. At the conclusion of the research and at your request, you generally will have access to your health information that Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research maintain in a designated record set, which means a set of data that includes medical information or billing records used in whole or in part by your doctors or other health care providers at Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research to make decisions about individuals. Access to your health information in a designated record set is described in the Notice of Privacy Practices provided to you by representatives of the specific institution where you are being enrolled into this research study which are: Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, DEPARTMENT OF DEFENSE CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, FDA, Baylor College of Medicine, data coordinating center, Data and Safety Monitoring Board, and TIRR: The Institute for Rehabilitation and Research may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: Christopher P. Smith, M.D.
 Scott Department of Urology
 Baylor College of Medicine
 One Baylor Plaza, BCM Stop 381,
 Houston, TX 77030

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

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Potential Risks and Discomforts

ONAbO NT-A: It is expected that you may have some or all of the following side effects when given ONAbO NT-A. Other side effects may occur which were not seen before. Side effects are usually temporary and manageable. However, it is possible they could cause serious disease or death. The study may include risks that are unknown at this time.

There have been rare reports of serious and/or immediate or even deadly abnormally sensitive reactions after treatment with ONAbO NT-A. These reactions include allergic reaction, skin rash, itching, swelling, and difficulty in breathing.

It is a rare possibility that the injection of ONAbO NT-A could lead to botulism. The classic symptoms of botulism include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. The doctor's examination may reveal that the gag reflex and the deep tendon reflexes like the knee jerk are decreased or absent.

There have been rare reports of sudden death, sometimes associated with difficulty in swallowing or pneumonia. There have also been rare reports of heart problems (including irregular heartbeats and heart attack, some resulting in death). Some of these patients already had or were at risk for heart disease. It is not known if ONAbO NT-A actually caused these problems.

It should not be used when infection is present at the injection site or if you are known to be abnormally sensitive to ONAbO NT-A.

The following events have been observed since ONAbO NT-A has been marketed: skin rash, itching, and allergic reaction. In general, these side effects occur within the first week following injection and, while usually temporary, they may last several months. Pain, tenderness, or bruising around the injection site may also occur. Local weakness of the injected muscle(s) is expected. Weakness of nearby muscles may also occur due to spread of ONAbO NT-A.

ONAbO NT-A contains albumin, which comes from human blood. Although the blood is rigorously tested, there is an extremely remote risk for the transmission of viruses and similar infectious agents.

OXYBUTYNIN ER: Common Side Effects: Blurred vision; constipation; diarrhea; dizziness; drowsiness; dry eyes, nose, skin, or mouth; headache; indigestion; nausea; runny nose; stomach pain or upset; trouble sleeping; weakness

Severe Side Effects: Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); confusion; difficult or painful urination; fast or irregular heartbeat; fever; hallucinations; mental or mood changes (e.g., agitation); seizures; swelling of the hands, ankles, or feet; vision problems.

Oxybutynin ER is contraindicated in patients with urinary retention, gastric retention and other severe

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decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin ER is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

The concomitant use of Oxybutynin ER with other anticholinergic drugs (used to relieve cramps or spasms of the stomach, intestines, and bladder) or with other agents that produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

The safety of Oxybutynin ER administered to women who are or who may become pregnant or are breastfeeding has not been established. Therefore, Oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

LIDOCAINE(R) (given to deaden the area around the injection site): The amount of Lidocaine that you will receive usually does not cause any side effects.

Rarely, the following side effects may be experienced:

- lightheadedness
- nervousness
- anxious or scared
- feeling of well being and great happiness
- confusion
- dizziness
- drowsiness
- ringing or buzzing in the ear
- blurred or double vision
- vomiting
- sensations of heat, cold or numbness
- slight jerking motions
- shaking
- convulsions or seizures
- loss of awareness of surroundings
- difficulty breathing or not breathing at all
- slow heart beat
- low blood pressure
- stopping of the heart

Extremely rare side effects include hives, swelling, and shock.

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PLACEBO: Since placebo has no active drug, your overactive bladder condition may become worse, stay the same or improve.

ANTIBIOTICS: An antibiotic may cause upset stomach, mild diarrhea, vomiting, and loss of appetite. Sensitivity to sunlight may increase. Please read the package insert that will be provided for additional information.

CYSTOSCOPY WITH BLADDER INJECTION: The discomfort is nearly identical to being catheterized, which generally causes slight to moderate discomfort. There will be a feeling of fullness in the bladder and a sensation to empty during the cystoscopy examination. Bleeding, infection, damage to urethra or surrounding structures may occur.

PVR: The risks of having a catheter placed in the bladder for draining the residual urine are infection of the urinary tract, injury to the urethra caused by rough insertion of the catheter, narrowing of the urethra due to scar tissue caused by the insertion of a catheter, injury to the bladder caused by incorrect insertion of the catheter.

URODYNAMICS: Generally the risks of an urodynamic study are low and are no more than those of a Foley Catheter insertion, which include the possibility of infection, trauma to the urethra or prostate, traumatic bleeding from the catheterization, discovery of previously unsuspected urethral stricture with inability to get the urodynamics catheter into the bladder.

Patients with a spinal cord injury generally occurring at the Thoracic 5 (T-5) level and above have a risk of experiencing autonomic dysreflexia during bladder filling during the urodynamic or study treatment procedures. Autonomic dysreflexia can develop suddenly, and is a possible emergency situation. Symptoms of autonomic dysreflexia include the following: elevation in blood pressure, headache, goose pimples, sweating above the level of injury, nasal congestion, slow pulse, blotching of the skin, and restlessness. If not treated promptly and correctly, it may lead to seizures, stroke, and in some cases, even death. To minimize this risk continuous blood pressure monitoring is performed throughout the study.

ULTRASOUND: Ultrasound testing is painless and harmless but the volunteer might experience anxiety in anticipation of the test. Ultrasound tests involve no radiation and studies have not revealed any adverse effects.

BLOOD DRAWS: Inserting needles into veins for collecting blood may be uncomfortable. Risks include slight bruising at the puncture site, fainting, the formation of a small blood clot or swelling of the vein and surrounding tissue, bleeding from the site, and the remote possibility of infection at the site of the needle puncture. Fainting is usually harmless, of short duration, and typically produces feelings of weakness, sweating, slowing of the heart rate and an abnormal decrease in blood pressure. Care will be taken to

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avoid these complications.

QUESTIONNAIRES: Completing the questionnaires may cause you to have or to experience some level of emotional discomfort due to the personal nature of the questions. The study doctor and staff will maintain a professional and caring attitude while administering the questionnaires.

LOSS OF CONFIDENTIALITY: The loss of confidentiality regarding research information is a possibility, although, the risk is extremely small. The investigator and his staff will make every effort to maintain the confidentiality. Your urine specimens will be labeled with your subject code before being sent to Dr. Chancellor's laboratory. The laboratory personnel will not be able to know that these specimens are yours. Study documents kept at Baylor College of Medicine (BCM) may include your initials and subject code but no other identifying information. Any of your information or specimens will not contain your initials if they leave BCM.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

The benefits of participating in this study may be: improvement in urinary incontinence symptoms, decrease in the occurrence of urinary tract infections, decrease in the number of required catheterizations, and an ease of the financial burden of buying protective garments. However, you may receive no benefit from participating.

Alternatives

The following alternative procedures or treatments are available if you choose not to participate in this study: oral medications or invasive surgery to enlarge your bladder with intestine.

Subject Costs and Payments

Standard of Care: Services provided at TIRR for this disease state include clinic visits, PVRs, Kidney ultrasounds (Visits 1 and End of Study), urodynamics studies, PSA, and urinalyses. These services will be billed/paid as normally done through TIRR.

Research Costs: The events and procedures that will be paid by the study sponsor are the pregnancy tests at Visits 1, 2, 4, 5, and 6, and all study medications.

You will receive \$50 for completing each of the study visits 2, 4, 5, and 6 for a total of \$200 if all visits are completed. In order for you to receive the stipend, you will provide your name, address, telephone number, and Social Security number. You will complete the BCM Research Participant/Donor Compensation form. A check will be mailed to you.

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Research Related Injury

If you experience a research related injury, please contact the Dr. Smith immediately at 713-798-4001. He will instruct you on what procedures to follow in order to receive treatment for the injury.

Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Women of Childbearing Potential

It is possible that the medicines used in this study could injure a fetus if you or your partner becomes pregnant while taking them. Because of the potential risks involved, you or your partner should not become pregnant while you are participating in this study.

If you are sexually active or become sexually active and can get pregnant or can get your partner pregnant, you must agree to use one of the following forms of birth control every time you have sex:

- * oral contraceptives ("the pill"),
- * intrauterine devices (IUDs),
- * contraceptive implants under the skin, or contraceptive injections,
- * condoms with foam.

Should you become pregnant while on this study, you must immediately notify the study personnel.

The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can choose not to provide this information.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, CHRISTOPHER PATRICK SMITH, and/or someone he/she appoints in his/her place

CONSENT FORM

HIPAA Compliant

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will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: CHRISTOPHER PATRICK SMITH at 713--798-4001 24 hours a day.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

SAMPLE STORAGE: You are being asked to agree to allow samples of your urine samples which will be stored as described in the Procedures section of this informed consent document, to be used for current research use. You are also being asked to agree to allow the use of stored materials for future research use. Complete confidentiality will be maintained and these samples will not be tracked back to you, except by using records available only to the Principal Investigators, the Co-Investigators, and your urologist.

PLEASE CIRCLE YOUR CHOICES AND INITIAL:

Samples used for current research: YES NO INITIALS

Samples used for future research: YES NO INITIALS

A description of this clinical trial (NCT010504114) will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this you also note that your child understands and agrees to take part in this study according to his or her understanding.

Please print your child's name here _____

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject Date

Legally Authorized Representative Date
Parent or Guardian

Investigator or Designee Obtaining Consent Date

Witness (if applicable) Date

Translator (if applicable) Date



Baylor College of Medicine
Office of Research
One Baylor Plaza, 600D
Houston, Texas 77030
Phone : (713) 798-6970
Fax: (713) 798-6990
Email: irb@bcm.tmc.edu

MEMORANDUM

TO: CHRISTOPHER PATRICK SMITH
UROLOGY

A handwritten signature in black ink, appearing to read "Flora M. Rivas", is positioned above the "FROM:" field.

FROM: FLOR MUNOZ-RIVAS, M.D.
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

DATE: July 11, 2017

RE: **H-34972 - A DOUBLE-BLIND, RANDOMIZED STUDY OF THE SAFETY AND EFFICACY OF ONABOTULINUMTOXINA (ONABONT-A) VERSUS ORAL OXYBUTYNIN IN SPINAL CORD INJURED PATIENTS WITH NEUROGENIC DETRUSOR OVERACTIVITY (PROTOCOL NUMBER 11-09-10-04) (TIRR)**

Your amendment, detailed below, was reviewed by Expedited procedures on July 11, 2017 by Board 3 and is now approved.

NOTE: Approved advertisement(s) should only be posted at the institution(s) where the research is being performed including approved recruitment site(s).

This is not applicable to the following advertisement modes: billboards, radio, television, internet, or website.

Description:

Protocol v.6/20/17

Inclusion Criteria, Section 7.1, page 16

Revised lower weight limit to 90 pounds.

It is noted that the consent form doesn't require revision.

The protocol is attached in Section S.

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ONAbO NT-A versus Oxybutynin ER in Patients with SCI and NDO

H-34972- A DOUBLE-BLIND, RANDOMIZED STUDY OF THE SAFETY AND EFFICACY OF ONABOTULINUMTOXINA (ONABONT-A) VERSUS ORAL OXYBUTYNIN IN SPINAL CORD INJURED PATIENTS WITH NEUROGENIC DETRUSOR OVERACTIVITY (PROTOCOL NUMBER 11-09-10-04) (TIRR)

Background

Please read this form carefully. In this consent form, "you" refers to you or your child.

Take time to ask the doctor or study staff as many questions about the study as you would like. If there are any words or information that you do not understand, the doctor or study staff will explain them to you. Reading this form and talking to the doctor or study staff may help you decide whether to participate or not. If you decide to take part in the study, you must sign and date the statement of consent and authorization on the last page of this form.

Neurogenic detrusor overactivity (NDO) is a condition in which the bladder is hyperactive, often resulting in urinary incontinence (UI - not able to control urine flow). A patient who has a spinal cord injury (SCI) often suffers with NDO.

Current treatment of UI resulting from NDO includes drugs that may help with the incontinence but they are likely to cause dry mouth, constipation and blurred vision.

ONAbO NT-A [BOTOX (R)] bladder injections have been studied in other clinical research trials in patients who have not responded to oral medications. The results have shown an improvement in how often urine leakage happens and an increase in the amount of urine the bladder can hold. ONAbO NT-A is approved by the FDA for bladder injections.

Oxybutynin ER (extended release) relaxes bladder smooth muscle. In patients with UI, studies have demonstrated that Oxybutynin ER increases bladder capacity, diminishes the frequency of urine loss, and delays the initial desire to urinate. Oxybutynin ER thus decreases urgency and the frequency of both incontinent episodes and voluntary urination. Oxybutynin ER is approved by the FDA for patients with UI.

You are being asked to participate in this clinical research study because you are a patient with a spinal cord injury and have NDO.

This research study is funded by the Department of Defense

Purpose

This purpose of this clinical trial is to see if ONAbO NT-A is safe and how well it works when injected into the bladder for the treatment of UI and if it works better than oxybutynin [Ditropan (R)] that is taken by mouth. A second purpose of the study is to perform research tests on your urine samples. Urine presents a rich source of information for bladder diseases and the biomarkers (the chemical make-up of the urine cells) will be examined to learn if there are yet undiscovered reasons for urinary diseases.

OPTIONAL RESEARCH: Future research projects using your urine samples may lead to better treatment of urinary diseases.

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Procedures

The research will be conducted at the following location(s):

Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research.

If you decide to be in this study, you will be asked to sign this informed consent document. You will be taking part in the study for at least 6-7 months and will visit the clinic at least 5 times.

This is a double blind study, which means that neither you nor your study doctor will know which study drugs you are receiving. However, your study doctor can get this information quickly in case of a health-related emergency.

You will be randomized to one of two treatments. The treatment you will be receiving is determined by random like the toss of a coin. You will have a 50-50 chance of receiving either treatment. The treatments are ARM 1: ONAbO NT bladder injection and one placebo (sugar pills) oral medication twice a day; or ARM 2: placebo (saline or salt water) bladder injection and Oxybutynin ER (like Ditropan) one capsule twice a day.

VISIT 1 - Screening

After your informed consent is obtained, the following will occur at least 2 weeks but not more than 4 weeks prior to Visit 2: randomization and bladder injection:

1. You will have a physical examination. The study staff will ask about your medical history including the medications you are now taking and procedures you have had.
2. Your vital signs (blood pressure, temperature and pulse rate) and weight will be measured.
3. You will have a kidney ultrasound or results of exam conducted within 1 year of enrollment. An ultrasound test is a radiology technique, which uses high -frequency sound waves to produce images of the organs and structures of the body. The sound waves are sent through body tissues with a device called a transducer. The transducer is placed directly on top of the skin, which has a gel applied to the surface. The sound waves that are sent by the transducer through the body are then reflected by internal structures as "echoes." These echoes return to the transducer and are transmitted electrically onto a viewing monitor. After the ultrasound, the gel is easily wiped off.
4. You will give about 3 teaspoons of blood to test the following:
 - To see if your blood count is normal.
 - If you are a female, to confirm that you are not pregnant.
 - Your PSA (Prostate specific antigen) which is a test used to screen for cancer of the prostate will be check if you are 50 years of age or older unless you have a family history or prostate cancer, or if you are of African American decent.. If so, the PSA will be checked if you are age 40 or older.
5. You will give a urine sample for routine tests.
6. You will complete the OAB-Patient Satisfaction with Treatment Questionnaire. It will take about 10 minutes for your to complete the questionnaire.
- 7 You will have urodynamic studies to give a baseline reading of what your bladder function is before

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you start the treatment. If you have had these studies within the past 12 months and you were not taking an medications for your overactive bladder, you will not need the studies at this visit. This test gives the doctors detailed information about the way your bladder and bladder outlet (the urethra) work when you try to urinate. It helps explain why you may have difficulty holding urine or urinary frequency . During this procedure, catheters with pressure sensors are placed through the urethra into your bladder and also into your rectum. The pressure in your bladder and rectum are measured while your bladder is filled with saline or dye solution. You will be asked questions about how full you feel and when you have the urge to urinate. You will be asked to urinate, if possible, during the study. X-rays and photos may be taken during the study.

8. If you are able to urinate, you will have a PVR (Post-Void Residual) test. The volume of fluid remaining in the bladder immediately after you urinate will be measured by catheterization (tube inserted into your bladder), or abdominal or vaginal ultrasound.

9. You will be given a bladder diary to keep track of the number of times you urinate , the amount, any leakage, etc. for 7 straight days in the week prior to next clinic visit.

10. You will be given a prescription for an antibiotic. You will take the antibiotic 3 days BEFORE your next visit, on the morning of the visit, and for 3 days AFTER the bladder injection.

11. You will be encouraged to stop taking any medications for overactive bladder symptoms for two weeks prior to the bladder injection.

VISIT 2: Randomization and Treatment (14 days to 6 weeks after Visit 1)

The following procedures and events will happen during this visit:

1. Your vital signs and weight will be measured.
2. If you are a female, you will provide a urine specimen to check for pregnancy. If the urine test is positive, you will give about 2 teaspoons of blood to check for pregnancy.
3. You will give a urine sample for routine tests and to use as a baseline for research testing .
4. If you are able to urinate, you will have a PVR.
5. The study doctor or a study staff member will review your current medications and ask about any problems you may have had since the last study visit.
6. You will be asked if you took any medications for your overactive bladder symptoms for the past two weeks.
7. You will complete the Incontinence Quality of Life questionnaire (I-QOL) and Incontinence Quality of Life neurogenic module (I-QOLNM) questionnaires prior to treatment. It will take about 15-20 minutes to complete the questionnaires.
8. Your bladder diary will be reviewed by the study staff. You will be given a bladder diary to keep track of the number of times you urinate, the amount, any leakage, etc. for 7 straight days in the week prior to next clinic visit.

You will be randomized into your treatment group.

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After randomization, the following events will occur:

8. Your bladder injection procedure will be done according to standard procedures in the clinic. The doctor will decide if you will be given a local anesthesia to lessen the pain before beginning the injection procedure. Your bladder will be filled with saline so that the area is free of urine. The injection will be given. The study doctor will discuss the procedure with you. After the injection, you will be observed for at least 30 minutes before you can go home. You will be instructed to continue your antibiotics for 3 more days.

9. You will be given the study oral medication dose while at the clinic and some to take home. You are to take the study medication as one capsule twice a day every day. You will be given a diary that you will complete to help you remember to take your medication. Please bring the pill bottle and the diary with you to your next clinic visit.

10. You will complete the bladder diary for 7 consecutive days in a row prior to next clinic visit in about 2 weeks.

VISIT 3: Telephone Visit (Day 3 to 5 after injection)

You will be contacted by telephone to discuss your well-being, any changes in your medications, your antibiotic compliance, and any side-effects or adverse events you may have experienced.

VISITS 4: Week 4 after injection (plus or minus 3 days)

1. Your vital signs and weight will be measured.
2. If you are able to urinate, you will have a PVR test.
3. If you are a female, you will provide a urine specimen to check for pregnancy. If the urine test is positive, you will give about 2 teaspoons of blood to check for pregnancy.
4. You will give a urine sample for routine tests and research testing.
5. Your bladder diary will be reviewed by the study staff. You will be given a bladder diary to keep track of the number of times you urinate, the amount, any leakage, etc. for 7 straight days in the week prior to next clinic visit.
6. The study doctor or a study staff member will review your medications and ask about any adverse events you may have had.
7. You will complete the I-QOL, I-QOLNM, OAB-Patient Satisfaction with Treatment Questionnaire (OAB_PSTQ), and Patient Global Assessment (PGA) questionnaires. It will take you about 20 to 30 minutes to complete them.
8. You will be given the study oral medication dose and the pill diary. Please bring the pill bottle and the diary with you to your next clinic visit.

VISIT 5: Week 12 after injection (plus or minus 3 days)

The procedures for this clinic visit are the same as VISIT 4. In addition, you will also undergo a

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urodynamic study as you did at Visit 1.

VISIT 6: Week 24: End of Study/Study Exit (2 weeks plus or minus 3 days after injection)

1. You will undergo a physical examination that includes your vital signs and weight measurements .
2. If you are able to urinate, you will have a PVR test.
3. You will give a urine sample for routine tests and research testing.
4. You will give about 3 teaspoons of blood to check your general health.
5. If you are a female, you will give about 2 teaspoons of blood to check for pregnancy.
6. You will give your completed bladder diary to the study doctor or staff.
7. The study doctor or a study staff member will review your medications and ask about any adverse events you may have had.
8. You will complete same 4 questionnaires as you did in VISIT 4.

This ends your participation in this research study.

If you are a male, you will have a total of approximately 6 teaspoons of blood drawn during the study. If you are a female, you will have a total of approximately 12 teaspoons of blood drawn during the study.

A portion of your urine samples will be sent to the Beaumont Research Institute at the Oakland University William Beaumont School of Medicine in Royal Oak, MI for research testing conducted under the supervision of Dr. Michael B. Chancellor. The samples will be coded so that only your study doctor will know how to link your name and other identifying information with the coded sample. The staff at the testing site will not be able to link the code to your information.

OPTIONAL RESEARCH:

With your permission, after research testing required for this study is completed, the remaining portion of your samples will be stripped of the code and will be banked for future use. It will be kept until it is all gone. Your samples will not be sold or transferred to anyone else but may be shared with the study doctor's colleagues for approved research studies. If at any time you withdraw from this study, you will not be able to get your urine samples back. You can't request that they be destroyed because the samples can't be linked to you.

Genetic testing will not be conducted on your specimens.

This institution does not plan to pay royalties to you if a commercial product is developed from blood or tissue obtained from you during this study.

You can participate in this study if you choose not to have your samples banked .

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Please see next to last page of this consent form to choose your choice for this optional research.

Research related health information

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document, you give permission to people who give medical care and ensure quality from Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Billing or financial records

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, TIRR: The Institute for Rehabilitation and Research, and DEPARTMENT OF DEFENSE CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS and their representatives.

Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. Agents of regulatory agencies such as the U.S. Department of Health and Human Services will be permitted to inspect the research records including your health information.

The data coordinating center will have access to the research records including your health information.

A Data and Safety Monitoring Board will have access to the research records including your health information.

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law .

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research are required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research to use and/or disclose (release) your health

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information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that the research involves treatment. You do not have to sign this Authorization, but if you do not, you may not receive research-related treatment. To maintain the integrity of this research study, you generally will not have access to your personal health information related to this research until the study is complete. However, your health information that is necessary to your care will be provided to you or your physician. At the conclusion of the research and at your request, you generally will have access to your health information that Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research maintain in a designated record set, which means a set of data that includes medical information or billing records used in whole or in part by your doctors or other health care providers at Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research to make decisions about individuals. Access to your health information in a designated record set is described in the Notice of Privacy Practices provided to you by representatives of the specific institution where you are being enrolled into this research study which are: Baylor College of Medicine and TIRR: The Institute for Rehabilitation and Research.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, DEPARTMENT OF DEFENSE CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, FDA, Baylor College of Medicine, data coordinating center, Data and Safety Monitoring Board, and TIRR: The Institute for Rehabilitation and Research may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: Christopher P. Smith, M.D.
 Scott Department of Urology
 Baylor College of Medicine
 One Baylor Plaza, BCM Stop 381,
 Houston, TX 77030

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

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Potential Risks and Discomforts

ONAbO NT-A: It is expected that you may have some or all of the following side effects when given ONAbO NT-A. Other side effects may occur which were not seen before. Side effects are usually temporary and manageable. However, it is possible they could cause serious disease or death. The study may include risks that are unknown at this time.

There have been rare reports of serious and/or immediate or even deadly abnormally sensitive reactions after treatment with ONAbO NT-A. These reactions include allergic reaction, skin rash, itching, swelling, and difficulty in breathing.

It is a rare possibility that the injection of ONAbO NT-A could lead to botulism. The classic symptoms of botulism include double vision, blurred vision, drooping eyelids, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. The doctor's examination may reveal that the gag reflex and the deep tendon reflexes like the knee jerk are decreased or absent.

There have been rare reports of sudden death, sometimes associated with difficulty in swallowing or pneumonia. There have also been rare reports of heart problems (including irregular heartbeats and heart attack, some resulting in death). Some of these patients already had or were at risk for heart disease. It is not known if ONAbO NT-A actually caused these problems.

It should not be used when infection is present at the injection site or if you are known to be abnormally sensitive to ONAbO NT-A.

The following events have been observed since ONAbO NT-A has been marketed: skin rash, itching, and allergic reaction. In general, these side effects occur within the first week following injection and, while usually temporary, they may last several months. Pain, tenderness, or bruising around the injection site may also occur. Local weakness of the injected muscle(s) is expected. Weakness of nearby muscles may also occur due to spread of ONAbO NT-A.

ONAbO NT-A contains albumin, which comes from human blood. Although the blood is rigorously tested, there is an extremely remote risk for the transmission of viruses and similar infectious agents.

OXYBUTYNIN ER: Common Side Effects: Blurred vision; constipation; diarrhea; dizziness; drowsiness; dry eyes, nose, skin, or mouth; headache; indigestion; nausea; runny nose; stomach pain or upset; trouble sleeping; weakness

Severe Side Effects: Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); confusion; difficult or painful urination; fast or irregular heartbeat; fever; hallucinations; mental or mood changes (e.g., agitation); seizures; swelling of the hands, ankles, or feet; vision problems.

Oxybutynin ER is contraindicated in patients with urinary retention, gastric retention and other severe

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decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin ER is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

The concomitant use of Oxybutynin ER with other anticholinergic drugs (used to relieve cramps or spasms of the stomach, intestines, and bladder) or with other agents that produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

The safety of Oxybutynin ER administered to women who are or who may become pregnant or are breastfeeding has not been established. Therefore, Oxybutynin chloride should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

LIDOCAINE(R) (given to deaden the area around the injection site): The amount of Lidocaine that you will receive usually does not cause any side effects.

Rarely, the following side effects may be experienced:

- lightheadedness
- nervousness
- anxious or scared
- feeling of well being and great happiness
- confusion
- dizziness
- drowsiness
- ringing or buzzing in the ear
- blurred or double vision
- vomiting
- sensations of heat, cold or numbness
- slight jerking motions
- shaking
- convulsions or seizures
- loss of awareness of surroundings
- difficulty breathing or not breathing at all
- slow heart beat
- low blood pressure
- stopping of the heart

Extremely rare side effects include hives, swelling, and shock.

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PLACEBO: Since placebo has no active drug, your overactive bladder condition may become worse, stay the same or improve.

ANTIBIOTICS: An antibiotic may cause upset stomach, mild diarrhea, vomiting, and loss of appetite. Sensitivity to sunlight may increase. Please read the package insert that will be provided for additional information.

CYSTOSCOPY WITH BLADDER INJECTION: The discomfort is nearly identical to being catheterized, which generally causes slight to moderate discomfort. There will be a feeling of fullness in the bladder and a sensation to empty during the cystoscopy examination. Bleeding, infection, damage to urethra or surrounding structures may occur.

PVR: The risks of having a catheter placed in the bladder for draining the residual urine are infection of the urinary tract, injury to the urethra caused by rough insertion of the catheter, narrowing of the urethra due to scar tissue caused by the insertion of a catheter, injury to the bladder caused by incorrect insertion of the catheter.

URODYNAMICS: Generally the risks of an urodynamic study are low and are no more than those of a Foley Catheter insertion, which include the possibility of infection, trauma to the urethra or prostate, traumatic bleeding from the catheterization, discovery of previously unsuspected urethral stricture with inability to get the urodynamics catheter into the bladder.

Patients with a spinal cord injury generally occurring at the Thoracic 5 (T-5) level and above have a risk of experiencing autonomic dysreflexia during bladder filling during the urodynamic or study treatment procedures. Autonomic dysreflexia can develop suddenly, and is a possible emergency situation. Symptoms of autonomic dysreflexia include the following: elevation in blood pressure, headache, goose pimples, sweating above the level of injury, nasal congestion, slow pulse, blotching of the skin, and restlessness. If not treated promptly and correctly, it may lead to seizures, stroke, and in some cases, even death. To minimize this risk continuous blood pressure monitoring is performed throughout the study.

ULTRASOUND: Ultrasound testing is painless and harmless but the volunteer might experience anxiety in anticipation of the test. Ultrasound tests involve no radiation and studies have not revealed any adverse effects.

BLOOD DRAWS: Inserting needles into veins for collecting blood may be uncomfortable. Risks include slight bruising at the puncture site, fainting, the formation of a small blood clot or swelling of the vein and surrounding tissue, bleeding from the site, and the remote possibility of infection at the site of the needle puncture. Fainting is usually harmless, of short duration, and typically produces feelings of weakness, sweating, slowing of the heart rate and an abnormal decrease in blood pressure. Care will be taken to

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avoid these complications.

QUESTIONNAIRES: Completing the questionnaires may cause you to have or to experience some level of emotional discomfort due to the personal nature of the questions. The study doctor and staff will maintain a professional and caring attitude while administering the questionnaires.

LOSS OF CONFIDENTIALITY: The loss of confidentiality regarding research information is a possibility, although, the risk is extremely small. The investigator and his staff will make every effort to maintain the confidentiality. Your urine specimens will be labeled with your subject code before being sent to Dr. Chancellor's laboratory. The laboratory personnel will not be able to know that these specimens are yours. Study documents kept at Baylor College of Medicine (BCM) may include your initials and subject code but no other identifying information. Any of your information or specimens will not contain your initials if they leave BCM.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

The benefits of participating in this study may be: improvement in urinary incontinence symptoms, decrease in the occurrence of urinary tract infections, decrease in the number of required catheterizations, and an ease of the financial burden of buying protective garments. However, you may receive no benefit from participating.

Alternatives

The following alternative procedures or treatments are available if you choose not to participate in this study: oral medications or invasive surgery to enlarge your bladder with intestine.

Subject Costs and Payments

Standard of Care: Services provided at TIRR for this disease state include clinic visits, PVRs, Kidney ultrasounds (Visits 1 and End of Study), urodynamics studies, PSA, and urinalyses. These services will be billed/paid as normally done through TIRR.

Research Costs: The events and procedures that will be paid by the study sponsor are the pregnancy tests at Visits 1, 2, 4, 5, and 6, and all study medications.

You will receive \$50 for completing each of the study visits 2, 4, 5, and 6 for a total of \$200 if all visits are completed. In order for you to receive the stipend, you will provide your name, address, telephone number, and Social Security number. You will complete the BCM Research Participant/Donor Compensation form. A check will be mailed to you.

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Research Related Injury

If you experience a research related injury, please contact the Dr. Smith immediately at 713-798-4001. He will instruct you on what procedures to follow in order to receive treatment for the injury.

Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Women of Childbearing Potential

It is possible that the medicines used in this study could injure a fetus if you or your partner becomes pregnant while taking them. Because of the potential risks involved, you or your partner should not become pregnant while you are participating in this study.

If you are sexually active or become sexually active and can get pregnant or can get your partner pregnant, you must agree to use one of the following forms of birth control every time you have sex:

- * oral contraceptives ("the pill"),
- * intrauterine devices (IUDs),
- * contraceptive implants under the skin, or contraceptive injections,
- * condoms with foam.

Should you become pregnant while on this study, you must immediately notify the study personnel.

The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can choose not to provide this information.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, CHRISTOPHER PATRICK SMITH, and/or someone he/she appoints in his/her place

CONSENT FORM

HIPAA Compliant

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

ONAbONT-A versus Oxybutynin ER in Patients with SCI and NDO

H-34972- A DOUBLE-BLIND, RANDOMIZED STUDY OF THE SAFETY AND EFFICACY OF ONABOTULINUMTOXINA (ONABONT-A) VERSUS ORAL OXYBUTYNIN IN SPINAL CORD INJURED PATIENTS WITH NEUROGENIC DETRUSOR OVERACTIVITY (PROTOCOL NUMBER 11-09-10-04) (TIRR)

will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: CHRISTOPHER PATRICK SMITH at 713--798-4001 24 hours a day.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

SAMPLE STORAGE: You are being asked to agree to allow samples of your urine samples which will be stored as described in the Procedures section of this informed consent document, to be used for current research use. You are also being asked to agree to allow the use of stored materials for future research use. Complete confidentiality will be maintained and these samples will not be tracked back to you, except by using records available only to the Principal Investigators, the Co-Investigators, and your urologist.

PLEASE CIRCLE YOUR CHOICES AND INITIAL:

Samples used for current research: YES NO INITIALS

Samples used for future research: YES NO INITIALS

A description of this clinical trial (NCT010504114) will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this you also note that your child understands and agrees to take part in this study according to his or her understanding.

Please print your child's name here _____

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject Date

Legally Authorized Representative Date
Parent or Guardian

Investigator or Designee Obtaining Consent Date

Witness (if applicable) Date

Translator (if applicable) Date

A Double-Blind, Randomized Study of Safety and Efficacy of OnabotulinumtoxinA (OnaBoNT-A) versus Oral Oxybutynin in SCI Patients with NDO (11-09-10-04)

SC110198; SCIRP-CTA-R

W81XWH-12-1-0549



PI: Christopher P. Smith, MD

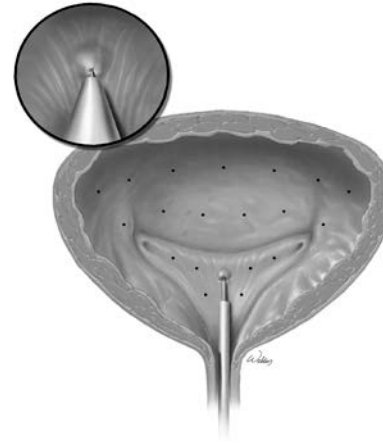
Org: Baylor College of Medicine Award Amount: 904,516.00

Study/Product Aim(s)

- Screen, enroll, and treat 36 patients randomized to two treatment groups
- Evaluation of biomarkers pretreatment and during follow up

Approach

FDA IND, BCM IRB, and MEDVAMC approvals were granted. HPRO approval with funding notice was received March 2013. The study was closed at MEDVAMC on July 25, 2016 due to lack of accrual. BCM IRB has approved the TIRR Memorial Hermann site and subject accrual is ongoing.



BOTOX Injection Pattern Diagram

Accomplishment: Thirteen patients have been consented at TIRR. Three have completed the study and three are being followed.

Timeline and Cost

Activities	FY	12	13	14	15	16
Regulatory Approvals		■				
Screening, Enrollment, Treatment			■	■	■	
Biomarker Evaluation			■	■	■	
Follow-up Visits			■	■	■	
Data Analysis/Reporting						■
Estimated Budget (\$K)		81	356	360	349	NCE

Goals/Milestones

CY12 Goal – Regulatory Affairs

- All required approvals are in place

CY13 Goals – Enrollment

- Advertisements have been placed and patient letters have been mailed

CY14 Goal – Subject visits and biomarker evaluations

- Accrual goals not met.

CY15 Goal – Subject visits and biomarker evaluations

- We will expand recruitment base at TIRR beginning in the 2nd Quarter.

CY16 Goal – Study Completion

- Subject follow-up visits , biomarker evaluation, and Data analysis/reporting completed

Comments/Challenges/Issues/Concerns

- Delayed enrollment due eligibility criteria

Budget Expenditure to Date

Projected Expenditure: \$270,000

Actual Expenditure: \$264,803

Updated: October 2017

SC110198: A Double-Blind, Randomized Study of the Safety and Efficacy of OnabotulinumtoxinA (OnaBoNT-A) versus Oral Oxybutynin in Spinal Cord Injured Patients with Neurogenic Detrusor Overactivity (Protocol Number 11-09-10-04)

STATEMENT OF WORK – October 13, 2017
START DATE March 12, 2013

Clinical Sites:

Site 1: Baylor College of Medicine
Scott Department of Urology
7200 Cambridge Street, Suite A10.152
Houston, TX 77030
PI: Christopher P. Smith, MD, MBA, MSS (CPS)
Study Coordinator: Sebrina Tello, CCRP (ST)

Site 2: TIRR Memorial Hermann
1333 Moursund Street
Houston, TX 77030
PI: Christopher P. Smith, MD, MBA, MSS (CPS)
Co-Investigators:
– John Ettore Bertini, Jr., MD, FACS
– Argyrios Stampas, MD
Study Coordinator: Sebrina Tello, CCRP (ST)

Research Laboratory:

Site 3: William Beaumont Hospital
Department of Urology
3811 West 13 Mile Road
Royal Oak, MI 48073
PI: Michael B. Chancellor, MD (MBC)
Laboratory Evaluations and Medical Monitor

Abbreviations: BCM = Baylor College of Medicine; TIRR = The Institute of Rehabilitation and Research;
WBH = William Beaumont Hospital

Specific Aims: (1) To evaluate the safety and efficacy of 200 U OnaBoNT-A injected into the detrusor versus oral oxybutynin for the treatment of urinary incontinence (UI) caused by neurogenic detrusor overactivity (NDO) in spinal cord injured volunteers; and (2) To determine the potential role of urine biomarkers as patient selection and surrogate endpoints of treatment outcome predictors.

Specific Aims 1&2: (1) To evaluate the safety and efficacy of 200 U OnaBoNT-A injected into the detrusor versus oral oxybutynin for the treatment of urinary incontinence (UI) caused by neurogenic detrusor overactivity (NDO) in spinal cord injured volunteers; and (2) To determine the potential role of urine biomarkers as patient selection and surrogate endpoints of treatment outcome predictors.	Research Sites		
	Timeline (Months)	BCM TIRR	WBH
Major Task 1: Submit regulatory documents and obtain approval for study start			
Subtask 1: IRB applications will be submitted	1-2		
Subtask 2: VA applications will be submitted	1-3		
Subtask 3: TIRR Research committee application submitted	36	CPS	
<i>Milestone Achieved: Local IRB* (VA) approval; (TIRR) approval</i>	(2) (34)		
<i>Milestone Achieved: MEDVAMC ACOS approval</i>	3		
<i>Milestone Achieved: HRPO** approval</i>	9		
Major Task 2: Screen, enroll, and treat 36 patients randomized to two treatment groups			
Subtask 1: Begin enrollment within 6 months after receiving grant	6	CPS/ST	
<i>Milestone Achieved: 1st participant consented (Lost to Follow-up)</i>	14		
Subtask 2: Enrollment to be performed	6 - 42	CPS/ST	
Subtask 3: All treatment and follow up to be performed	6 - 52	CPS/ST	
Major Task 3: Evaluation of biomarkers pretreatment and during follow up			
Subtask 1: Pretreatment	6 - 52		MBC
Subtask 2: Follow-up	6 - 52		MBC
Major Task 4: Data analysis and reporting			
Subtask 1: Data and safety monitoring will be ongoing	6 - 60	CPS	
Subtask 2: Final analysis will be completed	36 - 54	CPS	
Subtask 3: Publications developed	54 - 60	CPS	MBC

Projected Quarterly Enrollment

Target Enrollment Pilot Study (#1) (per quarter)***	Year 1				Year 2				Total
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
BCM	-	-	0	0	0	0	0	0	0
Target Enrollment (cumulative)	-	-	0	0	0	0	0	0	0

Target Enrollment Pilot Study (#1) (per quarter)	Year 3				Year 4				Year 5 (No Cost Extension)				Total
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
BCM (VA) Closed 7/25/16	0	0	0	0	0	0	0	0	0	0	0	0	0
BCM (TIRR)	0	0	0	0	0	0	2	1	3	0	0	0	6
Target Enrollment (cumulative)	0	0	0	0	0	0	12	12	12	0	0	0	36

* IRB = Institutional Review Board; committee formally designated to approve, monitor, and review human subjects research

** HRPO = Human Research Protection Office; review and approval by HRPO office of protocols involving human subjects is required of all DoD-funded awards

*** Target Enrollment = Enrollment will continue at both sites until the accrual goal has been met. There is no specific total for each site.