Award Number: W81XWH-12-1-0549

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)

PRINCIPAL INVESTIGATOR: Christopher P. Smith, MD

CONTRACTING ORGANIZATION: Baylor College of Medicine
Houston, TX 77030

REPORT DATE: October 2015

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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Christopher P. Smith, MD

E-Mail: cps@bcm.edu

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Baylor College of Medicine
One Baylor Plaza, T100
Houston, TX 77030-3498

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U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

No subjects have been treated as yet. Recruitment at Michael E. DeBakey VAMC has been difficult due to eligibility criteria. Dr. Smith plans to open patient recruitment to a new site with a large spinal cord injury population, The Institute of Rehabilitation and Research (TIRR). The BCM IRB initial approval of the addition of the TIRR Memorial Hermann site has been approved. The application to the Memorial Hermann Office of Research has been submitted and approval is awaiting final budget agreement. Once the study has been approved by Memorial Hermann, the HPRO will be notified. Recruitment will begin after HPRO approval is received.

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

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Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

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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 15 mg per day of oral oxybutynin hydrocholoride ER in 36 spinal cord injured veterans who visit the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) and those 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.

KEYWORDS

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

OVERALL PROJECT SUMMARY

Previously, one patient was consented but did not respond to repeated attempts to contact him to set his screening visit appointment. He is considered lost to follow-up.

Protocol v.4/30/15 revisions include:

- Recruitment Process – page 19: Added: Trifold pamphlets
- Screening - Visit 1 – page 20
  - Was: Urodynamic Studies: The volunteer will then be placed in the sitting position and the pressure transducers will be leveled with the pubic symphysis. The pressure transducers will be zeroed to atmospheric pressure as reference point.
  - Now: The volunteer will then be placed in the sitting position and the pressure transducers will be leveled with the pubic symphysis.
- Screening - Visit 1 – page 20: Added: Dispense Antibiotic: If subject has an allergy to Cipro or if urine culture indicates Cipro resistant, another drug may be substituted.

IRB actions since the 2014 annual report submission include the following:

- 14Apr2014 Amendment submission for revised brochure
- 21Apr2014 IRB amendment approval, informed consent document (ICD),
- 06Oct2014 Amendment submission for revised HIPAA form
- 26Nov2014 IRB amendment approval, ICD, and HIPAA approved form
- 21Jan2015 IRB annual renewal submission
- 07Feb2015 IRB renewal approval and ICD
- 27May2015 Amendment submission for Protocol v.4/30/15
- 22Jun2015 IRB amendment approval, ICD, and brochure

This past year, 598 charts were reviewed and discussed in SCI Rounds. Theses patient where not eligible for our study due to the following:

- 54 patients do not meet Inclusion #6
- 100 patients do not meet Inclusion #7
- 140 patients do not meet Inclusion #10
- 94 patients do not meet Inclusion #11
- 8 patients met Exclusion #1
- 6 patients met Exclusion #3
- 7 patients met Exclusion #8
- 1 patient met Exclusion #16
- 7 patients met Exclusion #19
- 1 patient diagnosed with renal cell carcinoma
- 174 patients' charts indicate non-Texas residents
- 6 could not or would not participate for various reasons

KEY RESEARCH ACCOMPLISHMENTS: Nothing to report

CONCLUSIONS

The BCM IRB initial approval of the addition of the TIRR Memorial Hermann site has been approved. The application to the Memorial Hermann Office of Research has been submitted and approval is awaiting final budget agreement. Once the study has been approved by Memorial Hermann, the HPRO will be notified. Recruitment will begin after HPRO approval is received.

The study budget and the sub-award are being finalized and it is hoped that enrollment will begin by the end of 2015.

It is noted that per e-mail request of Dr. Henry, the grant's Science Officer, an updated SOW is included to this annual report.

PUBLICATIONS ABSTRACTS AND PRESENTATIONS: None

INVENTIONS, PATENTS AND LICENSES: None

REPORTABLE OUTCOMES: None

OTHER ACHIEVEMENTS: None

REFERENCES: None

APPENDICES

- Protocol v.4/30/15
  - Changes document
  - Protocol's tracked changes
  - Full protocol

- IRB Documents noted above
- QUADCHART: Attached
- SOW updated 10/18/15

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

AMENDMENT

Protocol Number:	H-26296
Principal Investigator:	CHRISTOPHER PATRICK SMITH
Initial Submit Date:	05/24/2012
Amendment Submit Date:	04/14/2014
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)

Reason: Other Amendment

Description: Approval of already approved brochure so it can be used at MEDVAMC Research Week.

Section J2 reads, 'Brochures may be placed in the clinic area to help draw attention to the clinical research study.' It has been edited to include, 'The brochures will be used a posters during the MEDVAMC Research Week.'

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: GABRIEL HABIB, M.D.
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

DATE: April 21, 2014

RE: **H-26296 - 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)**

Your amendment, detailed below, has been reviewed and 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:
Approval of already approved brochure so it can be used at MEDVAMC Research Week.

Section J2 reads, 'Brochures may be placed in the clinic area to help draw attention to the clinical research study.' It has been edited to include, 'The brochures will be used a posters during the MEDVAMC Research Week.'

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

OnaBoNT-A versus Oxybutynin ER in Patients (Veterans) with SCI and NDO

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.

OnaBoNT-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. OnaBoNT-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 veteran with a spinal cord injury and have NDO.

This study is funded by the sponsor, the Department of Defense.

Purpose

This purpose of this clinical trial is to see if onaBoNT-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, Michael E. DeBakey Veterans Affairs Medical Center.

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: onaBoNT bladder injection and a placebo (sugar pill) oral medication once a day; or ARM 2: placebo (saline or salt water) bladder injection and Oxybutynin ER (like Ditropan) capsule once 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 6 months of Visit 1. 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 and to use as a baseline for research testing.

6. 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 six 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.

7. 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.

8. 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.

9. 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.

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, your 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 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.
7. 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 wll 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 once 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, your 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.

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, your give about 2 teaspoons of blood to confirm that you are not pregnant.
6. You will have a kidney ultrasound.
7. You will give your completed bladder diary to the study doctor or staff.
8. The study doctor or a study staff member will review your medications and ask about any adverse events you may have had.
9. 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.

Your research doctor may never be able to provide you with your research related health information.

Potential Risks and Discomforts

OnaBoNT-A: It is expected that you 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.

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 heart beats 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 onaBoNT-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 onaBoNT-A.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

The following events have been observed since onaBoNT-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 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.

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.

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® (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, diarrhea, vomiting, skin rash, itching, hives, difficulty breathing or swallowing, wheezing, unusual bleeding or bruising, sore throat, painful mouth or throat sores, and vaginal infection. 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 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 CONFIENTIALITY: 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 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 Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) 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 MEDVAMC.

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. 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. Both males and females should use birth control.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study.

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 the MEDVAMC 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 the MEDVAMC.

Research Costs: The events and procedures that will be paid by the study sponsor are the kidney ultrasound at Visit 2, the pregnancy tests at Visits 1, 2, 4, 5, and 6 and all study medications.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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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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.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

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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.

Your Health Information

Your signature on this form means that you give permission for the use and disclosure of your protected health information for this research study. Federal law requires that the Michael E. Debakey Veterans Affairs Medical Center protect health information linked to your identity. The procedures section above provides the specific information and the person(s) who would use or disclose it.

If you decide not to give your permission for the use and disclosure of your protected health information as we have described for this study, you will receive access to the same treatment, payment, enrollment or eligibility for benefits as you normally would.

People who give medical care and ensure quality from the institutions where the research is being done, the sponsor(s) listed in the sections above, representatives of the sponsor, and regulatory agencies such as the U.S. Department of Health and Human Services will be allowed to look at sections of your medical and research records related to this study. Because of the need for the investigator and study staff to release information to these parties, complete privacy cannot be guaranteed.

If you decide to take part in the study, your protected health information will not be given out except as allowed by the regulations or as described in this form. The results of the data from the study may be published. However, you will not be identified by name. People who receive your protected health information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by laws governing them.

You may decide that you no longer allow protected health information that identifies you to be used or disclosed for this research study. Contact the study staff to tell them of this decision, and they will give you an address so that you can inform the investigator in writing. The investigator will honor this decision unless the researchers have already acted in reliance on your information. Then it will not be possible to honor your decision in this way.

The people listed above will be able to access your information for as long as they need to, even after the study is completed.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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 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.

Under Federal Regulations, the VA Medical facility shall provide necessary medical treatment to you as a research subject injured as a result by participation in a research project approved by a VA Research and Development Committee and conducted under the supervision of one or more VA employees. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. If you sustain an injury as a direct result of your study participation, medical care will be provided by the Michael E. DeBakey VA Medical Center. The Department of Veterans Affairs does not normally provide any other form of compensation for injury. You do not waive any liability rights for personal injury by signing this form.

You may withdraw from this study at any time without penalty or loss of VA or other benefits to which you are entitled. Your participation will not affect the way you now pay for medical care at the VAMC. If you would like to verify the validity of the study and authorized contacts, you may speak with the Michael E. DeBakey Veterans Affairs Medical Center Research Office at 713-794-7918 or 713-794-7566.

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

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

Samples used for future research: ____YES ____NO _____INITIALS

Department of Veterans Affairs

VA RESEARCH CONSENT FORM

HIPAA Compliant

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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 Date

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

AMENDMENT

Protocol Number:	H-26296
Principal Investigator:	CHRISTOPHER PATRICK SMITH
Initial Submit Date:	05/24/2012
Amendment Submit Date:	10/06/2014
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)

Reason: Other Amendment

Description: The MEDVAMC has an updated template for the HIPAA Authorization form. As instructed by Mary Reid, attached in Section S is the updated form. Mary has reviewed and approved the form.

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: GABRIEL HABIB, M.D.
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

DATE: November 26, 2014

RE: **H-26296 - 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)**

Your amendment, detailed below, has been reviewed and 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:
The MEDVAMC has an updated template for the HIPAA Authorization form. As instructed by Mary Reid, attached in Section S is the updated form. Mary has reviewed and approved the form.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

OnaBoNT-A versus Oxybutynin ER in Patients (Veterans) with SCI and NDO

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.

OnaBoNT-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. OnaBoNT-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 veteran with a spinal cord injury and have NDO.

This study is funded by the sponsor, the Department of Defense.

Purpose

This purpose of this clinical trial is to see if onaBoNT-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, Baylor College of Medicine, Michael E. DeBakey Veterans Affairs Medical Center.

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: onaBoNT bladder injection and a placebo (sugar pill) oral medication once a day; or ARM 2: placebo (saline or salt water) bladder injection and Oxybutynin ER (like Ditropan) capsule once 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 6 months of Visit 1. 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 and to use as a baseline for research testing.
6. 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 six 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.
7. 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.
8. 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.
9. 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.

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, your 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 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.
7. 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 wll 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 once 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, your 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.

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, your give about 2 teaspoons of blood to confirm that you are not pregnant.
6. You will have a kidney ultrasound.
7. You will give your completed bladder diary to the study doctor or staff.
8. The study doctor or a study staff member will review your medications and ask about any adverse events you may have had.
9. 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.

Your research doctor may never be able to provide you with your research related health information.

Potential Risks and Discomforts

OnaBoNT-A: It is expected that you 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.

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 heart beats 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 onaBoNT-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 onaBoNT-A.

The following events have been observed since onaBoNT-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 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.

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.

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® (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, diarrhea, vomiting, skin rash, itching, hives, difficulty breathing or swallowing, wheezing, unusual bleeding or bruising, sore throat, painful mouth or throat sores, and vaginal infection. 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 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 CONFIENTIALITY: 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 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 Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) 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 MEDVAMC.

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. 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. Both males and females should use birth control.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study.

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 the MEDVAMC 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 the MEDVAMC.

Research Costs: The events and procedures that will be paid by the study sponsor are the kidney ultrasound at Visit 2, the pregnancy tests at Visits 1, 2, 4, 5, and 6 and all study medications.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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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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.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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.

Your Health Information

Your signature on this form means that you give permission for the use and disclosure of your protected health information for this research study. Federal law requires that the Michael E. Debakey Veterans Affairs Medical Center protect health information linked to your identity. The procedures section above provides the specific information and the person(s) who would use or disclose it.

If you decide not to give your permission for the use and disclosure of your protected health information as we have described for this study, you will receive access to the same treatment, payment, enrollment or eligibility for benefits as you normally would.

People who give medical care and ensure quality from the institutions where the research is being done, the sponsor(s) listed in the sections above, representatives of the sponsor, and regulatory agencies such as the U.S. Department of Health and Human Services will be allowed to look at sections of your medical and research records related to this study. Because of the need for the investigator and study staff to release information to these parties, complete privacy cannot be guaranteed.

If you decide to take part in the study, your protected health information will not be given out except as allowed by the regulations or as described in this form. The results of the data from the study may be published. However, you will not be identified by name. People who receive your protected health information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by laws governing them.

You may decide that you no longer allow protected health information that identifies you to be used or disclosed for this research study. Contact the study staff to tell them of this decision, and they will give you an address so that you can inform the investigator in writing. The investigator will honor this decision unless the researchers have already acted in reliance on your information. Then it will not be possible to honor your decision in this way.

The people listed above will be able to access your information for as long as they need to, even after the study is completed.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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 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.

Under Federal Regulations, the VA Medical facility shall provide necessary medical treatment to you as a research subject injured as a result by participation in a research project approved by a VA Research and Development Committee and conducted under the supervision of one or more VA employees. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. If you sustain an injury as a direct result of your study participation, medical care will be provided by the Michael E. DeBakey VA Medical Center. The Department of Veterans Affairs does not normally provide any other form of compensation for injury. You do not waive any liability rights for personal injury by signing this form.

You may withdraw from this study at any time without penalty or loss of VA or other benefits to which you are entitled. Your participation will not affect the way you now pay for medical care at the VAMC. If you would like to verify the validity of the study and authorized contacts, you may speak with the Michael E. DeBakey Veterans Affairs Medical Center Research Office at 713-794-7918 or 713-794-7566.

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

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

Samples used for future research: ____YES ____NO _____INITIALS

Department of Veterans Affairs

VA RESEARCH CONSENT FORM

HIPAA Compliant

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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	Date

Department of Veterans Affairs	**Authorization for Use & Release of Individually Identifiable Health Information for Veterans Health Administration (VHA) Research**

Subject Name (Last, First, Middle Initial):	**Subject SSN** (last 4 only):	**Date of Birth:**

VA Facility (Name and Address):

Michael E. DeBakey VA Medical Center (MEDVAMC)
2002 Holcombe Blvd.
Houston, Texas 77030

VA Principal Investigator (PI):	**PI Phone Contact Information:**
Christopher P. Smith, MD	7113-798-4001

Study Number & Title:

H-26296: A Double-Blind, Randomized Study of the Safety and Efficacy of OnabotulinumtoxinA (onaBoNT-A) versus Oral Oxybutynin ER in Spinal Cord Injured Patients with Neurogenic Detrusor Overactivity (Protocol Number 11-09-10-04)

Purpose of Study:

The purpose is to see if onaBoNT-A is safe and how well it works when injected into the bladder for the treatment of urinary incontinence and if it works better than oxybutynin [Ditropan (R)]. A second purpose of the study is to perform research tests on your urine samples.

USE OF YOUR INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION (IIHI):

Your individually identifiable health information is information about you that contains your health information and information that would identify you such as your name, date of birth, or other individual identifiers. VHA is asking you to allow the VA Principal Investigator (PI) and /or the VA research team members to access and use your past or present health information in addition to new health information they may collect for the study named above. The investigators of this study are committed to protecting your privacy and the confidentiality of information related to your health care.

Signing this authorization is completely voluntary. However, your authorization (permission) is necessary to participate in this study. Your treatment, payment, enrollment, or eligibility for VA benefits will not be affected, whether or not you sign this authorization.

Your individually identifiable health information used for this VA study includes the information marked below:

☑ Information from your VA Health Records such as diagnoses, progress notes, medications, lab or radiology findings, etc.

Specific information concerning:

☐ alcohol abuse ☐ drug abuse ☐ sickle cell anemia ☐ HIV

☑ Demographic Information such as name, age, race, etc.

☐ Billing or Financial Records

☐ Photographs, Videotapes, and/or Audiotapes of you

☑ Questionnaire, Survey, and/or Subject Diary

☐ Other, as described :

Authorization for Use & Release of Individually Identifiable Health Information for Veterans Health Administration (VHA) Research

Subject Name (Last, First, Middle Initial)**:**	**Subject SSN** (last 4 only)**:**	**Date of Birth:**

USE OF YOUR DATA OR SPECIMENS FOR OTHER VA/VHA RESEARCH: (This section must only be completed when banking is a required component of this study. When banking in a **VHA** repository is an optional component of this study complete page 4 of this form in lieu of this section.) Use page five for **NON-VA/VHA** Repository.

☑ Not Applicable – Banking of identifiable data/specimens is not required

An important part of this research is to save your ☐ Data ☐ Specimen in a secure VHA repository/bank for other research studies in the future. If you do not agree to allow this use of your data and/or specimen for future studies approved by the required committees, such as the Institutional Review Board, you will not be able to participate in this study.

DISCLOSURE: The VA research team may need to disclose the information listed above to other people or institutions that are not part of VA. VA/VHA complies with the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), Privacy Act of 1974 and all other applicable federal laws and regulations that protect your privacy. The VHA Notice of Privacy Practices (a separate document) provides more information on how we protect your information. If you do not have a copy of the Notice, the research team will provide one to you.

Giving your permission by signing this authorization allows us to disclose your information to other institutions or persons outside the VA/VHA as noted below. Once your information has been disclosed outside VA/VHA, it may no longer be protected by federal laws and regulations and might be re-disclosed by the persons or institutions receiving the information. These non-VA/VHA institutions or persons include the entities marked below:

☑ Baylor College of Medicine, Office of Research- will monitor the study

☐ Study Sponsor (name):
Person or entity who takes responsibility for and initiates a clinical investigation

☑ Academic Affiliate (institution/name/employee/department): Baylor College of Medicine
A relationship with VA in the performance of this study

☐ Federal Drug Administration (FDA)-Federal Agency required to monitor & oversee research

☑ Department of Health & Human Services-Federal Agency required to monitor & oversee research

Other (name and specific purpose):

Scott Department of Urology Research Administration's Regulatory and Clinical Research Affairs,

located at BCM is responsible for all regulatory documents and communications between the BCM IRB

Affiliated Institutions' committees, and the FDA.

Authorization for Use & Release of Individually Identifiable Health Information for Veterans Health Administration (VHA) Research

Subject Name (Last, First, Middle Initial):	**Subject SSN** (last 4 only):	**Date of Birth:**

Note: *Offices within VA/VHA that are responsible for oversight of VA research such as the Office of Research Oversight (ORO), the Office of Research and Development (ORD), the VA Office of Inspector General, the VA Office of General Counsel, the VA IRB and Research and Development Committee may also have access to your information in the performance of their VA/VHA job duties.*

REVOCATION: If you sign this authorization you may change your mind and revoke or take back your permission at any time. You must do this in writing and must send your written request to the Principal Investigator for this study at the following address:

Christopher P. Smith, MD

MICHAEL E. DEBAKEY VA MEDICAL CENTER
2002 HOLCOMBE BLVD. MAILCODE: 112
HOUSTON, TEXAS 77030

If you revoke (take back) your permission, you will no longer be able to participate in this study but the benefits to which you are entitled will NOT be affected. If you revoke (take back) your permission, the research team may continue to use or disclose the information that it has already collected before you revoked (took back) your permission which the research team has relied upon for the research. Your written revocation is effective as soon as it is received by the study's Principal Investigator.

EXPIRATION: Unless you revoke (take back) your permission, your authorization to allow us to use and/or disclose your information will: (may select more than one if there is a VHA data/specimen repository)

☑ Expire at the end of this main research study

☐ Expire on the following date or event: _____

☐ The data and/or specimens in a VHA repository or registry will not have an expiration date.

TO BE FILLED OUT BY THE SUBJECT

Research Subject Signature. This permission (authorization) has been explained to me and I have been given the opportunity to ask questions. If I believe that my privacy rights have been compromised, I may contact the VHA facility Privacy Officer to file a verbal or written complaint. I give my authorization (permission) for the use and disclosure of my individually identifiable health information as described in this form. I will be given a signed copy of this form for my records.

_____ _____
Signature of Research Subject Date

_____ _____
Signature of Legal Representative (if applicable) Date

To Sign for Research Subject (Attach authority to sign: Health Care Power of Attorney, Legal Guardian appointment, or Next of Kin if authorized by State Law)

_____ _____
Name of Legal Representative (please print) Date

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

RENEWAL

Protocol Number: H-26296
Principal Investigator: CHRISTOPHER PATRICK SMITH
Initial Submit Date: 05/24/2012
Renewal Submit Date: 01/21/2015
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)

SUBJECTS
During your last approval period, you were approved to enroll 36 subjects locally and 36 subjects worldwide.

Race/Ethnicity	Male	Female
All Ethnicities	0	0
American Indian Or Alaskan Native	0	0
Asian/Non Vietnamese	0	0
Black Or African American	0	0
Hispanic Or Latino	0	0
Mixed Race Or Ethnicity	0	0
Native Hawaiian Or Pacific Islander	0	0
Vietnamese	0	0
White	0	0

LOCAL: 0
WORLDWIDE: 0

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
No subjects were enrolled during the last year. Only one subject has been enrolled to this study, but was withdrawn because he did not respond to requests to make an appointment for the screening visit.. He was entered onto the master list of subjects for the study. He signed the consent form prior to undergoing any study interactions or interventions. This subject was not considered a member of any vulnerable populations. Three hundred and twenty-three charts have been reviewed. Of those, 69 met inclusion #6, 73 meet inclusion #7, 86 met inclusion #10, 39 met inclusion #11, 4 met exclusion #1, 1 met exclusion #2, 3 met exclusion #8, 41 lived out of state, and the rest could not or would not participate for various reasons. We will continue to review charts during the coming year and visit the Spinal Cord Unit in order to identify patients that might be eligible to participate. We have not had any adverse events, unanticipated problems involving risks to subjects or others; therefore, there were no SAEs (whether related or unrelated to the research) reported to the IRB.

RISK/BENEFIT RATIO
The potential benefits continue to 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: 3/2/2015 6:01:17 AM) (Sort Order: Amendment Date)

Amendment Submit Date: 10/06/2014
Reason: Other Amendment
Description: The MEDVAMC has an updated template for the HIPAA Authorization form. As instructed by Mary Reid, attached in Section S is the updated form. Mary has reviewed and approved the form.

Amendment Submit Date: 04/14/2014
Reason: Other Amendment
Description: Approval of already approved brochure so it can be used at MEDVAMC Research Week. Section J2 reads, 'Brochures may be placed in the clinic area to help draw attention to the clinical research study.' It has been edited to include, 'The brochures will be used a posters during the MEDVAMC Research Week.'

Amendment Submit Date: 11/20/2013
Reason: Multiple Amendments
Description: 1. Informed consent has been revised to remove unneccessary spaces and language. There appears to be a 'period' in the printed (or print view) that is not appropriate. We are not able to remove it. 2. The DOD has requested that the sentence regarding the study's sponsor by revised. This sentence is at the end of the Background section. 3. All advertising has been revised to indicate the study coordinator's new telephone number at the VA and replacing of the BCM logo.

Amendment Submit Date: 11/01/2013
Reason: Other Amendment
Description: Addition of PHI being collected in order to provide the subjects' stipends. Sections H, L and Qj have been revised.

Amendment Submit Date: 07/05/2013
Reason: Multiple Amendments
Description: Protocol v. 6/12/13 Protocol Changes from 4-30-13 to 6-12-13 Purpose – page 15 Was: At baseline, each follow-up period, and after a two week washout 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. Now: 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. Clarification of detrusor overactivity: Eligibility – Inclusion #7, page 17 Was: 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 Day 1 (prior to randomization, or if within 3 months of screening if patient is off antimuscarinic/anticholinergic drugs at the time of urodynamic testing). Now: 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 6 months of screening if patient is off antimuscarinic/ anticholinergic drugs at the time of urodynamic testing). Recruitment Process, page 19 Advertising brochures will be placed in the Urology Clinic; included in the MEDVAMC newsletter; and included in a mail out planned for potential subjects. An advertisement will be placed on the Craig's List website. Study Procedures 10.1 Screening - Visit 1, page 19 Was: Urodynamic studies: Now: Urodynamic studies (if not performed 6

months prior to the Randomization Visit): 10.3 Post Randomization/Treatment Visits (Follow Up), page 23 Was: Post Randomization/Treatment Visits (Follow Up) (Day 3 (± 3 days) weeks, and 6, 9, 12, 18, 24, and 26 months post randomization/treatment) Now: Post Randomization/Treatment Visits (Follow Up) -Day 3, and Weeks 4, 12, and 24 (± 3 days) post randomization/treatment 10.3.2 Visit 4, page 23 Was: Visits 4, 5, and 7: Weeks 4, 8, and 16 (± 3 days) post randomization/treatment Now: Week 4 (± 3 days) post randomization/treatment 10.3.3. Visit 5, page 23 Was: Visit 6: Week 12 (± 3 days) post randomization/treatment Now: Visit 5: Week 12 (± 3 days) post randomization/treatment 10.3.4. Visit 8 Week 20 (± 3 days) post randomization/treatment, page 23 Deleted study visit 10.3.5. End of Study Visit, page 23 Was: Visit 10: Week 26 (± 3 days) post Visit 9 - End of Study Visit Now: Visit 6: Week 24 (± 3 days) post randomization/treatment - End of Study Visit Was: Urodynamic studies no longer required at End of Study Visit Now: Urodynamic studies no longer required at End of Study Visit CMP (Complete Metabolic Panel) has been added. Data Analysis, page 24 Was: Additionally, we will look at the longitudinal pattern of the questionnaires at baseline, 4, 8 and 12 weeks…. Now: Additionally, we will look at the longitudinal pattern of the questionnaires at baseline, 4, and 12 weeks…. Subject Stipend Section 17: Withdrawal from Study, page 32 Was: Volunteers participating in this study will not receive any payment for their participation. Now: Volunteers participating in this study will receive $50 for completing each of the study visits 2, 4, 5, and 6. Schedule of Events: Appendix I, page 41 Advertising: BCM website revision, Brochure, Patient Letter, and Craig's List ad

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Amendment Submit Date: 07/05/2013
Reason: Multiple Amendments
Description: Protocol v. 6/12/13 Protocol Changes from 4-30-13 to 6-12-13 Purpose – page 15 Was: At baseline, each follow-up period, and after a two week washout 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. Now: 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. Clarification of detrusor overactivity: Eligibility – Inclusion #7, page 17 Was: 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 Day 1 (prior to randomization, or if within 3 months of screening if patient is off antimuscarinic/anticholinergic drugs at the time of urodynamic testing). Now: 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 6 months of screening if patient is off antimuscarinic/ anticholinergic drugs at the time of urodynamic testing). Recruitment Process, page 19 Advertising brochures will be placed in the Urology Clinic; included in the MEDVAMC newsletter; and included in a mail out planned for potential subjects. An advertisement will be placed on the Craig's List website. Study Procedures 10.1 Screening - Visit 1, page 19 Was: Urodynamic studies: Now: Urodynamic studies (if not performed 6 months prior to the Randomization Visit): 10.3 Post Randomization/Treatment Visits (Follow Up), page 23 Was: Post Randomization/Treatment Visits (Follow Up) (Day 3 (± 3 days) weeks, and 6, 9, 12, 18, 24, and 26 months post randomization/treatment) Now: Post Randomization/Treatment Visits (Follow Up) -Day 3, and Weeks 4, 12, and 24 (± 3 days) post randomization/treatment 10.3.2 Visit 4, page 23 Was: Visits 4, 5, and 7: Weeks 4, 8, and 16 (± 3 days) post randomization/treatment Now: Week 4 (± 3 days) post

randomization/treatment 10.3.3. Visit 5, page 23 Was: Visit 6: Week 12 (± 3 days) post randomization/treatment Now: Visit 5: Week 12 (± 3 days) post randomization/treatment 10.3.4. Visit 8 Week 20 (± 3 days) post randomization/treatment, page 23 Deleted study visit 10.3.5. End of Study Visit, page 23 Was: Visit 10: Week 26 (± 3 days) post Visit 9 - End of Study Visit Now: Visit 6: Week 24 (± 3 days) post randomization/treatment - End of Study Visit Was: Urodynamic studies no longer required at End of Study Visit Now: Urodynamic studies no longer required at End of Study Visit CMP (Complete Metabolic Panel) has been added. Data Analysis, page 24 Was: Additionally, we will look at the longitudinal pattern of the questionnaires at baseline, 4, 8 and 12 weeks…. Now: Additionally, we will look at the longitudinal pattern of the questionnaires at baseline, 4, and 12 weeks…. Subject Stipend Section 17: Withdrawal from Study, page 32 Was: Volunteers participating in this study will not receive any payment for their participation. Now: Volunteers participating in this study will receive $50 for completing each of the study visits 2, 4, 5, and 6. Schedule of Events: Appendix I, page 41 Advertising: BCM website revision, Brochure, Patient Letter, and Craig's List ad

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Amendment Submit Date: 07/05/2013
Reason: Protocol no longer actively enrolling
Description: Protocol v. 6/12/13 Protocol Changes from 4-30-13 to 6-12-13 Purpose – page 15 Was: At baseline, each follow-up period, and after a two week washout 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. Now: 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. Clarification of detrusor overactivity: Eligibility – Inclusion #7, page 17 Was: 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 Day 1 (prior to randomization, or if within 3 months of screening if patient is off antimuscarinic/anticholinergic drugs at the time of urodynamic testing). Now: 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 6 months of screening if patient is off antimuscarinic/ anticholinergic drugs at the time of urodynamic testing). Recruitment Process, page 19 Advertising brochures will be placed in the Urology Clinic; included in the MEDVAMC newsletter; and included in a mail out planned for potential subjects. An advertisement will be placed on the Craig's List website. Study Procedures 10.1 Screening - Visit 1, page 19 Was: Urodynamic studies: Now: Urodynamic studies (if not performed 6 months prior to the Randomization Visit): 10.3 Post Randomization/Treatment Visits (Follow Up), page 23 Was: Post Randomization/Treatment Visits (Follow Up) (Day 3 (± 3 days) weeks, and 6, 9, 12, 18, 24, and 26 months post randomization/treatment) Now: Post Randomization/Treatment Visits (Follow Up) -Day 3, and Weeks 4, 12, and 24 (± 3 days) post randomization/treatment 10.3.2 Visit 4, page 23 Was: Visits 4, 5, and 7: Weeks 4, 8, and 16 (± 3 days) post randomization/treatment Now: Week 4 (± 3 days) post randomization/treatment 10.3.3. Visit 5, page 23 Was: Visit 6: Week 12 (± 3 days) post randomization/treatment Now: Visit 5: Week 12 (± 3 days) post randomization/treatment 10.3.4. Visit 8 Week 20 (± 3 days) post randomization/treatment, page 23 Deleted study visit 10.3.5. End of Study Visit, page 23 Was: Visit 10: Week 26 (± 3 days) post Visit 9 - End of Study Visit Now: Visit 6: Week 24 (± 3 days) post randomization/treatment - End of Study Visit Was: Urodynamic studies no longer required at End of Study Visit Now: Urodynamic studies no longer required at End of Study Visit CMP

(Complete Metabolic Panel) has been added. Data Analysis, page 24 Was: Additionally, we will look at the longitudinal pattern of the questionnaires at baseline, 4, 8 and 12 weeks…. Now: Additionally, we will look at the longitudinal pattern of the questionnaires at baseline, 4, and 12 weeks…. Subject Stipend Section 17: Withdrawal from Study, page 32 Was: Volunteers participating in this study will not receive any payment for their participation. Now: Volunteers participating in this study will receive $50 for completing each of the study visits 2, 4, 5, and 6. Schedule of Events: Appendix I, page 41 Advertising: BCM website revision, Brochure, Patient Letter, and Craig's List ad

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Amendment Submit Date: 05/29/2013
Reason: Multiple Amendments
Description: Protocol v.4/30/13 changes: 1. Clarification of time frame for washout period for antimuscarinic/anticholinergic drugs: Eligibility – Inclusion #7, page 17 Was: 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 Day 1 (prior to randomization). Now: 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 Day 1 (prior to randomization, or if within 3 months of screening if patient is off antimuscarinic/anticholinergic drugs at the time of urodynamic testing). Eligibility – Exclusion #2, page 18 Was: Volunteer has had previous or current botulinum toxin therapy of any serotype for any urological condition or, treatment within 6 months of Randomization/Day 1 for any other condition or use Now: Volunteer has had previous or current botulinum toxin therapy of any serotype for any urological condition within 9 months or, treatment within 3 months of Randomization/Day 1 for any other condition or use. 2. Bladder ultrasound no longer required: 10.1, page 19; 10.3.4, page 23; and 10.3.6, page 24 Was: Bladder and Kidney ultrasounds Now: Kidney ultrasound or results of exam conducted within 6 months of Visit 1. The HPR and ICD have been revised to reflect these changes.

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Reason: Multiple Amendments
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Amendment Submit Date: 01/31/2013
Reason: Other Amendment
Description: This protocol is being funded by the DOD. For research determined to be greater than minimal risk, DODI 3216.02 requires that the IRB approve, by name, an independent research monitor with expertise consonant with the nature of risk(s) identified within the research protocol. The IRB must

approve a written summary of the monitors' duties, authorities, and responsibilities. The research monitor's duties should be based on specific risks or concerns about the research. The research monitor may perform oversight functions and report their observations and findings to the IRB or a designated official. The research monitor may be identified from within or outside the PI's institution. Donald P. Griffith, MD, Chief of the Urology Service at MEDVAMC, is the research monitor for this study. As part of his function as Chief, he has participated in many clinical research studies and is aware of the concerns for the protection of human research subjects. He has knowledge of the mechanisms of the two study agents (onabotulinumtoxinA and oxybutynin). His research monitor functions may include: • observing recruitment and enrollment procedures and the consent process, • discussing with the investigators with regards to the protocol's study interventions and interactions, • reviewing monitoring plans and UPIRTSO reports; • reviewing data matching, data collection, and analysis In addition, Dr. Griffith shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. He shall also have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO. Dr. Griffith's CV and CITI MEDVAMC human subject's protection training documentation is attached in Section S.

Amendment Submit Date: 01/31/2013
Reason: Other Amendment
Description: This protocol is being funded by the DOD. For research determined to be greater than minimal risk, DODI 3216.02 requires that the IRB approve, by name, an independent research monitor with expertise consonant with the nature of risk(s) identified within the research protocol. The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities. The research monitor's duties should be based on specific risks or concerns about the research. The research monitor may perform oversight functions and report their observations and findings to the IRB or a designated official. The research monitor may be identified from within or outside the PI's institution. Donald P. Griffith, MD, Chief of the Urology Service at MEDVAMC, is the research monitor for this study. As part of his function as Chief, he has participated in many clinical research studies and is aware of the concerns for the protection of human research subjects. He has knowledge of the mechanisms of the two study agents (onabotulinumtoxinA and oxybutynin). His research monitor functions may include: • observing recruitment and enrollment procedures and the consent process, • discussing with the investigators with regards to the protocol's study interventions and interactions, • reviewing monitoring plans and UPIRTSO reports; • reviewing data matching, data collection, and analysis In addition, Dr. Griffith shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. He shall also have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO. Dr. Griffith's CV and CITI MEDVAMC human subject's protection training documentation is attached in Section S.

Amendment Submit Date: 06/19/2012
Reason: Other Amendment
Description: The VA Biomedical Laboratory Research and Development Service has requested the following changes: In the consent form: - Please indicate if the specimens will be shared with other researchers for other approved research protocols. - Please disclose any potential commerical benefits and if the subject will receive additional money or other benefits from future testing on their specimens. - Please indicate that no genetic testing will be performed on specimens. - Clarify coding system. Changes to the HPR: - Clarify coding

system of specimens sent to Dr. Chancellor. All requested changes have been completed.

February 27, 2015

CHRISTOPHER PATRICK SMITH
BAYLOR COLLEGE OF MEDICINE
UROLOGY

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

H-26296 - 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)

APPROVAL VALID FROM 2/27/2015 TO 2/9/2016

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 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,

GABRIEL HABIB, M.D.
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

OnaBoNT-A versus Oxybutynin ER in Patients (Veterans) with SCI and NDO

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.

OnaBoNT-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. OnaBoNT-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 veteran with a spinal cord injury and have NDO.

This study is funded by the sponsor, the Department of Defense.

Purpose

This purpose of this clinical trial is to see if onaBoNT-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, Michael E. DeBakey Veterans Affairs Medical Center.

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: onaBoNT bladder injection and a placebo (sugar pill) oral medication once a day; or ARM 2: placebo (saline or salt water) bladder injection and Oxybutynin ER (like Ditropan) capsule once 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 6 months of Visit 1. 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 and to use as a baseline for research testing.
6. 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 six 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.
7. 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.
8. 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.
9. 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.

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, your 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 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.
7. 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 wll 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 once 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, your 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.

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, your give about 2 teaspoons of blood to confirm that you are not pregnant.
6. You will have a kidney ultrasound.
7. You will give your completed bladder diary to the study doctor or staff.
8. The study doctor or a study staff member will review your medications and ask about any adverse events you may have had.
9. 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.

Your research doctor may never be able to provide you with your research related health information.

Potential Risks and Discomforts

OnaBoNT-A: It is expected that you 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.

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 heart beats 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 onaBoNT-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 onaBoNT-A.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

The following events have been observed since onaBoNT-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 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.

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.

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® (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, diarrhea, vomiting, skin rash, itching, hives, difficulty breathing or swallowing, wheezing, unusual bleeding or bruising, sore throat, painful mouth or throat sores, and vaginal infection. 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.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

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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.

LOSS OF CONFIENTIALITY: 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 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 Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) 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 MEDVAMC.

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. 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. Both males and females should use birth control.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study.

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 the MEDVAMC 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 the MEDVAMC.

Research Costs: The events and procedures that will be paid by the study sponsor are the kidney ultrasound at Visit 2, the pregnancy tests at Visits 1, 2, 4, 5, and 6 and all study medications.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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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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.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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.

Your Health Information

Your signature on this form means that you give permission for the use and disclosure of your protected health information for this research study. Federal law requires that the Michael E. Debakey Veterans Affairs Medical Center protect health information linked to your identity. The procedures section above provides the specific information and the person(s) who would use or disclose it.

If you decide not to give your permission for the use and disclosure of your protected health information as we have described for this study, you will receive access to the same treatment, payment, enrollment or eligibility for benefits as you normally would.

People who give medical care and ensure quality from the institutions where the research is being done, the sponsor(s) listed in the sections above, representatives of the sponsor, and regulatory agencies such as the U.S. Department of Health and Human Services will be allowed to look at sections of your medical and research records related to this study. Because of the need for the investigator and study staff to release information to these parties, complete privacy cannot be guaranteed.

If you decide to take part in the study, your protected health information will not be given out except as allowed by the regulations or as described in this form. The results of the data from the study may be published. However, you will not be identified by name. People who receive your protected health information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by laws governing them.

You may decide that you no longer allow protected health information that identifies you to be used or disclosed for this research study. Contact the study staff to tell them of this decision, and they will give you an address so that you can inform the investigator in writing. The investigator will honor this decision unless the researchers have already acted in reliance on your information. Then it will not be possible to honor your decision in this way.

The people listed above will be able to access your information for as long as they need to, even after the study is completed.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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 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.

Under Federal Regulations, the VA Medical facility shall provide necessary medical treatment to you as a research subject injured as a result by participation in a research project approved by a VA Research and Development Committee and conducted under the supervision of one or more VA employees. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. If you sustain an injury as a direct result of your study participation, medical care will be provided by the Michael E. DeBakey VA Medical Center. The Department of Veterans Affairs does not normally provide any other form of compensation for injury. You do not waive any liability rights for personal injury by signing this form.

You may withdraw from this study at any time without penalty or loss of VA or other benefits to which you are entitled. Your participation will not affect the way you now pay for medical care at the VAMC. If you would like to verify the validity of the study and authorized contacts, you may speak with the Michael E. DeBakey Veterans Affairs Medical Center Research Office at 713-794-7918 or 713-794-7566.

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

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

Samples used for future research: ____YES ____NO _____INITIALS

Department of Veterans Affairs

VA RESEARCH CONSENT FORM

HIPAA Compliant

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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	Date

Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

AMENDMENT

Protocol Number: H-26296
Principal Investigator: CHRISTOPHER PATRICK SMITH
Initial Submit Date: 05/24/2012
Amendment Submit Date: 05/27/2015
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)

Reason: Multiple Amendments

Description: Protocol v. 4/30/15

Recruitment Process – page 19: Added: Trifold pamphlets

Screening - Visit 1 – page 20

Was: Urodynamic Studies: The volunteer will then be placed in the sitting position and the pressure transducers will be leveled with the pubic symphysis. The pressure transducers will be zeroed to atmospheric pressure as reference point.

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

Screening - Visit 1 – page 20

Added: Dispense Antibiotic: If subject has an allergy to Cipro or if urine culture indicates Cipro resistant, another drug may be substituted.

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: GABRIEL HABIB, M.D.
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

DATE: June 22, 2015

RE: **H-26296 - 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)**

Your amendment, detailed below, has been reviewed and 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. 4/30/15

Recruitment Process – page 19: Added: Trifold pamphlets

Screening - Visit 1 – page 20

Was: Urodynamic Studies: The volunteer will then be placed in the sitting position and the pressure transducers will be leveled with the pubic symphysis. The pressure transducers will be zeroed to atmospheric pressure as reference point.

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Subject Name: _____ **Date:** _____

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Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

OnaBoNT-A versus Oxybutynin ER in Patients (Veterans) with SCI and NDO

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.

OnaBoNT-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. OnaBoNT-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 veteran with a spinal cord injury and have NDO.

This study is funded by the sponsor, the Department of Defense.

Purpose

This purpose of this clinical trial is to see if onaBoNT-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, Michael E. DeBakey Veterans Affairs Medical Center.

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: onaBoNT bladder injection and a placebo (sugar pill) oral medication once a day; or ARM 2: placebo (saline or salt water) bladder injection and Oxybutynin ER (like Ditropan) capsule once 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 6 months of Visit 1. 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 and to use as a baseline for research testing.
6. 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 six 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.
7. 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.
8. 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.
9. 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.

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, your 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 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.
7. 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 wll 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 once 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, your 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.

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, your give about 2 teaspoons of blood to confirm that you are not pregnant.
6. You will have a kidney ultrasound.
7. You will give your completed bladder diary to the study doctor or staff.
8. The study doctor or a study staff member will review your medications and ask about any adverse events you may have had.
9. 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.

Your research doctor may never be able to provide you with your research related health information.

Potential Risks and Discomforts

OnaBoNT-A: It is expected that you 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.

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 heart beats 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 onaBoNT-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 onaBoNT-A.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

The following events have been observed since onaBoNT-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 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.

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.

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® (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, diarrhea, vomiting, skin rash, itching, hives, difficulty breathing or swallowing, wheezing, unusual bleeding or bruising, sore throat, painful mouth or throat sores, and vaginal infection. 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.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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.

LOSS OF CONFIENTIALITY: 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 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 Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) 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 MEDVAMC.

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. 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. Both males and females should use birth control.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study.

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 the MEDVAMC 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 the MEDVAMC.

Research Costs: The events and procedures that will be paid by the study sponsor are the kidney ultrasound at Visit 2, the pregnancy tests at Visits 1, 2, 4, 5, and 6 and all study medications.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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.

.

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.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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.

Your Health Information

Your signature on this form means that you give permission for the use and disclosure of your protected health information for this research study. Federal law requires that the Michael E. Debakey Veterans Affairs Medical Center protect health information linked to your identity. The procedures section above provides the specific information and the person(s) who would use or disclose it.

If you decide not to give your permission for the use and disclosure of your protected health information as we have described for this study, you will receive access to the same treatment, payment, enrollment or eligibility for benefits as you normally would.

People who give medical care and ensure quality from the institutions where the research is being done, the sponsor(s) listed in the sections above, representatives of the sponsor, and regulatory agencies such as the U.S. Department of Health and Human Services will be allowed to look at sections of your medical and research records related to this study. Because of the need for the investigator and study staff to release information to these parties, complete privacy cannot be guaranteed.

If you decide to take part in the study, your protected health information will not be given out except as allowed by the regulations or as described in this form. The results of the data from the study may be published. However, you will not be identified by name. People who receive your protected health information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by laws governing them.

You may decide that you no longer allow protected health information that identifies you to be used or disclosed for this research study. Contact the study staff to tell them of this decision, and they will give you an address so that you can inform the investigator in writing. The investigator will honor this decision unless the researchers have already acted in reliance on your information. Then it will not be possible to honor your decision in this way.

The people listed above will be able to access your information for as long as they need to, even after the study is completed.

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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 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.

Under Federal Regulations, the VA Medical facility shall provide necessary medical treatment to you as a research subject injured as a result by participation in a research project approved by a VA Research and Development Committee and conducted under the supervision of one or more VA employees. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. If you sustain an injury as a direct result of your study participation, medical care will be provided by the Michael E. DeBakey VA Medical Center. The Department of Veterans Affairs does not normally provide any other form of compensation for injury. You do not waive any liability rights for personal injury by signing this form.

You may withdraw from this study at any time without penalty or loss of VA or other benefits to which you are entitled. Your participation will not affect the way you now pay for medical care at the VAMC. If you would like to verify the validity of the study and authorized contacts, you may speak with the Michael E. DeBakey Veterans Affairs Medical Center Research Office at 713-794-7918 or 713-794-7566.

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

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

Samples used for future research: ____YES ____NO _____INITIALS

VA RESEARCH CONSENT FORM

HIPAA Compliant

Subject Name: _____ **Date:** _____

Subject Initials: _____

Principal Investigator: CHRISTOPHER PATRICK SMITH **VAMC:** _____

H-26296 - 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)

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	Date

You will receive financial compensation for your time and travel of $50 for each study visit (2, 4-6) for a total $200 if you complete all visits.

For more information, call Sebrina Tello at 713-791-1414 Ext. 25326

MICHAEL E. DEBAKEY VETERANS AFFAIRS MEDICAL CENTER

Are you a Veteran with a

Spinal Cord Injury

and you are you are having Overactive Bladder symptoms?

Volunteers are need for a Clinical Research Study

Baylor College of Medicine

GIVING LIFE TO POSSIBLE

H-26296

Do you suffer from symptoms of a bladder that is hyperactive resulting in unwanted urine flow?

Are you a veteran 18 to 80 years old?

Have you had your spinal cord injury for more than 6 months?

Do you leak in between intermittent catherization?

Are you able to complete a bladder diary?

Then you may qualify for this research study.

You will have 5 clinic visits and 1 telephone visit during this study.

Your participation in the study will be about 6 to 7 months.

H-26296: A Multicenter, Double-Blind, Randomized Study of the Safety and Efficacy of Botulinum Toxin Type A (BoNT-A) versus Oral Oxybutynin in Spinal Cord Injured Patients with Neurogenic Detrusor Overactivity (Protocol Number 11-09-10-04)

Protocol Changes from 6-12-13 to 4-30-15

Recruitment Process – page 19

Added: Trifold pamphlets

Screening - Visit 1 – page 20

Was: Urodynamic Studies: The volunteer will then be placed in the sitting position and the pressure transducers will be leveled with the pubic symphysis. The pressure transducers will be zeroed to atmospheric pressure as reference point.

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

Screening - Visit 1 – page 20

Added: Dispense Antibiotic: If subject has an allergy to Cipro or if urine culture indicates Cipro resistant, another drug may be substituted.

Study Procedures

10.1 Screening - Visit 1, page 19

Was: Urodynamic studies:

Now: Urodynamic studies (if not performed 6 months prior to the Randomization Visit):

10.3 Post Randomization/Treatment Visits (Follow Up), page 23

Was: Post Randomization/Treatment Visits (Follow Up) (Day 3 (± 3 days) weeks, and 6, 9, 12, 18, 24, and 26 months post randomization/treatment)

Now: Post Randomization/Treatment Visits (Follow Up) -Day 3, and Weeks 4, 12, and 24 (± 3 days) post randomization/treatment

10.3.2 Visit 4, page 23

Was: Visits 4, 5, and 7: Weeks 4, 8, and 16 (± 3 days) post randomization/treatment

Now: Week 4 (± 3 days) post randomization/treatment

10.3.3. Visit 5, page 23

Was: Visit 6: Week 12 (± 3 days) post randomization/treatment

Now: Visit 5: Week 12 (± 3 days) post randomization/treatment

10.3.4. Visit 8 Week 20 (± 3 days) post randomization/treatment, page 23

Deleted study visit

10.3.5. End of Study Visit, page 23

Was: Visit 10: Week 26 (± 3 days) post Visit 9 - End of Study Visit

Now: Visit 6: Week 24 (± 3 days) post randomization/treatment - End of Study Visit

Was: Urodynamic studies no longer required at End of Study Visit

Now: Urodynamic studies no longer required at End of Study Visit

CMP (Complete Metabolic Panel) has been added.

Data Analysis, page 25

Was: Additionally, we will look at the longitudinal pattern of the questionnaires at baseline, 4, 8 and 12 weeks….

Now: Additionally, we will look at the longitudinal pattern of the questionnaires at baseline, 4, and 12 weeks….

Subject Stipend

Section 17: Withdrawal from Study, page 32

Was: Volunteers participating in this study will not receive any payment for their participation.

Now: Volunteers participating in this study will receive $50 for completing each of the study visits 2, 4, 5, and 6.

Schedule of Events

Appendix I, page 41

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)

Protocol Version: ~~June 12, 2013~~April 30, 2015

PHASE 3B

PRINCIPAL INVESTIGATOR: **Christopher P. Smith MD, MBA**
Associate Professor
Scott Department of Urology
Baylor College of Medicine
1709 Dryden Street, Suite 16.10
Houston, TX 77030
E-mail: cps@bcm.edu

CO-INVESTIGATORS: **Timothy B. Boone, MD, PhD**
Methodist Urology Associates
The Methodist Hospital Physician Organization
6560 Fannin, Suite 2100
Houston, TX 77030
E-Mail: tboone3@tmhs.org

Michael B. Chancellor, MD
Clinical Professor,
Oakland University William Beaumont School of Medicine
3535 West 13 Mile Road, Suite 438
Royal Oak, MI 48073
E-mail: Michael.chancellor@beaumont.edu

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

BCM IRB NUMBER: H-26296

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 the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) in Houston, TX. 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 and trifold pamphlets will be placed in the Urology Clinic; included in the MEDVAMC newsletter; and included in a mail out planned for potential subjects. An advertisement will be placed on the Craig's List website.

All potential volunteers that meet the inclusion and exclusion criteria will be offered enrollment in the study. Volunteers that present as a result of the website registration will be referred directly to Dr. Smith.

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 BCM's ICD provides a signature line for a volunteer's Legally Authorized Representative if applicable. The veteran population is literate and speak English; therefore, provisions are not available for consenting populations who are not. Each patient executing an informed consent document will be given a unique consecutive number beginning with the number 001.

The VA Research HIPAA Authorization Form will be executed for each subject.

All subjects will be entered onto the master list of subjects for the study after signing a consent form and prior to undergoing any study interactions or interventions.

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 6 months of Visit 1.
- Post void residual (PVR) in volunteers who micturate or have a mixed catheterization/micturition pattern
- Urine specimen to conduct urinalysis, urine culture and sensitivity, and biomarker evaluation (See Appendix III)
- CBC (Complete Blood Count)
- CMP (Complete Metabolic Panel)
- Pregnancy test - serum (for females only)
- Prostate specific antigen (for males only)
- Urodynamic studies (if not performed 6 months 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 pressure transducers will be zeroed to atmospheric pressure as reference point.~~

  The pressures bladder (Pves) and rectum (Pabd) are measured while the bladder is filled with saline at 50ml/min. The urodynamic machine will also record the subtracted detrusor pressure (Pdet=Pves – Pabd). Where the Pabd pressure is adjusted at baseline to render Pdet =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 urodynamist 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 [Cipro (generic is permissible) 500 mg 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 Cipro or if urine culture indicates Cipro resistant, another drug may be substituted.

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 (± 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 Visit 4: Week 4 (± 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.
- Serum pregnancy test (females)
- 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 (± 3 days) post randomization/treatment

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

~~10.3.5. Visit 9: Week 24 (± 3 days) post randomization/treatment~~

~~10.3.6. Visit 10: Week 26 (± 3 days) post Visit 9 - End of Study Visit~~

10.3.4. Visit 6: Week 24 (± 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
- Kidney ultrasound
- Study drug accountability
- Collect bladder diary

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, ~~8,~~ 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 baseline and each study visit. 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.

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 MEDVAMC 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

Under Federal Regulations, a VA Medical facility shall provide necessary medical treatment to a research volunteer injured as a result by participation in a research project approved by a VA Research and Development Committee and conducted under the supervision of one or more VA employees. This requirement does not apply to treatment for injuries that result from non-compliance by a research volunteer with study procedures. If an injury as a direct result of study participation is sustained, medical care will be provided by the VA Medical facility. The Department of Veterans Affairs does not normally provide any other form of compensation for injury.

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 not receive any payment for their participation.~~ 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

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 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
Post void residual	X	X		X	X	X
Kidney ultrasound within 6 months	X					X
Urodynamic studies within 6 months and off meds for 2 weeks prior to urodynamic studies	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
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
Patient Global Assessment				X	X	X
Adverse event assessments		X	X	X	X	X
Subject stipend for transportation		X		X	X	X

Non-standard of care is highlighted in yellow.

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)

Protocol Version: April 30, 2015

PHASE 3B

PRINCIPAL INVESTIGATOR: **Christopher P. Smith MD, MBA**
Associate Professor
Scott Department of Urology
Baylor College of Medicine
1709 Dryden Street, Suite 16.10
Houston, TX 77030
E-mail: cps@bcm.edu

CO-INVESTIGATORS: **Timothy B. Boone, MD, PhD**
Methodist Urology Associates
The Methodist Hospital Physician Organization
6560 Fannin, Suite 2100
Houston, TX 77030
E-Mail: tboone3@tmhs.org

Michael B. Chancellor, MD
Clinical Professor,
Oakland University William Beaumont School of Medicine
3535 West 13 Mile Road, Suite 438
Royal Oak, MI 48073
E-mail: Michael.chancellor@beaumont.edu

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

BCM IRB NUMBER: H-26296

TABLE OF CONTENTS

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 veterans 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 (onaBoNT-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, onaBoNT-A's denervating effects are widespread. In fact, onaBoNT-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 onaBoNT-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 H_2O, $p<0.016$) in 21 patients with NDO that were injected with onaBoNT-A. [Schurch et al, 2000] A strong impetus driving industry sponsored clinical trials examining the effects of onaBoNT-A on NDO was provided by the first randomized, placebo-controlled trial examining the effects of two doses of onaBoNT-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 onaBoNT-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 onaBoNT-A (300 U) in 57 patients with urinary incontinence resulting from MS or SCI. At 6 weeks following treatment, onaBoNT-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 onaBoNT-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 onaBoNT-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 onaBoNT-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 onaBoNT-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_2O)	14 $\pm$ 2	29 $\pm$ 5	0.002
Maximum cystometric capacity (mL)	322 $\pm$ 32	421 $\pm$ 33	0.008
Maximum det/ves pressure (cm H_2O)	59 $\pm$ 4	36 $\pm$ 5	<0.001
Reflex detrusor volume (mL)	155 $\pm$ 22	187 $\pm$ 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 H_2O (mean 14 $\pm$ 2ml/cm H_2O). In this subset of 22 patients, baseline compliance increased 260% post-treatment, from a mean of 11.2 $\pm$ 1 to 29.2 $\pm$ 5 ml/cm H_2O, 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 H_2O with reduction of MDP into the normal range in 9/18 (50%) after onaBoNT-A therapy. Overall, the mean MDP decreased from 59 $\pm$ 4 to 36 $\pm$ 5 cm H_2O.

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 $\pm$ 1 to 29.2 $\pm$ 5 ml/cm H_2O, p=0.001**

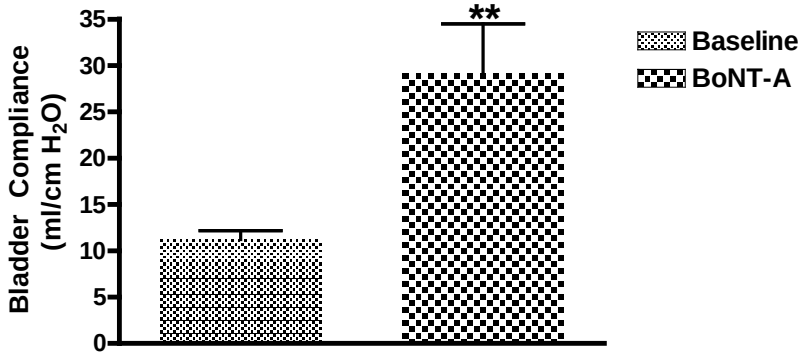


Figure 2. Bladder Compliance

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 CX_3C) 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 ± 1.5	0.1 ± 0.1	
Week 1				
1. ASB and non UTI	13	8.3 ± 2.1	0.2 ± 0.1	*p* =0.01*
2. Symptomatic UTI	5	77.8 ± 17.3	1.1 ± 0.5	*p* =0.79#
Week 2				
1. ASB and non UTI	9	5.1 ± 1.8	0.1 ± 0.1	*p*<0.01*
2. Prev. symptomatic UTI treated with ABX and now asymptomatic	5	12.8 ± 8.8	0.2 ± 0.2	*p*=0.04 **
3. New onset Symptomatic UTI	4	85.6 ±42.2	1.3 ± 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+/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-2Rα, 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 onaBoNT-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 (onaBoNT-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. OnaBoNT-A **(**onabotulinumtoxin A, Botox®, Allergan Inc., Irvine, CA)

OnaBoNT-A will be the active formulation. Each vial of onaBoNT-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 heart beats 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 15 mg capsule will be taken 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 one compounding pharmacy or the MEDVAMC Research 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 15 mg per day of oral oxybutynin hydrocholoride 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. They are veterans who visit the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) 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 MEDVAMC Research Pharmacy to either: ARM 1: onaBoNT-A 200 U bladder injection and placebo oral capsule daily or ARM 2: Placebo bladder injection (saline) and oxybutynin ER 15mg capsule 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 6 months of screening if patient is off antimuscarinic/anticholinergic drugs at the time of urodynamic testing.
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 than1year) from screening.

2. Volunteer has had previous or current botulinum toxin therapy of any serotype for any urological condition within 9 months or, treatment within 3 months of Randomization/Day 1 for any other condition or use.
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 or has a 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.
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/Day1.
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 the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC) in Houston, TX. 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 and trifold pamphlets will be placed in the Urology Clinic; included in the MEDVAMC newsletter; and included in a mail out planned for potential subjects. An advertisement will be placed on the Craig's List website.

All potential volunteers that meet the inclusion and exclusion criteria will be offered enrollment in the study. Volunteers that present as a result of the website registration will be referred directly to Dr. Smith.

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 BCM's ICD provides a signature line for a volunteer's Legally Authorized Representative if applicable. The veteran population is literate and speak English; therefore, provisions are not available for consenting populations who are not. Each patient executing an informed consent document will be given a unique consecutive number beginning with the number 001.

The VA Research HIPAA Authorization Form will be executed for each subject.

All subjects will be entered onto the master list of subjects for the study after signing a consent form and prior to undergoing any study interactions or interventions.

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 6 months of Visit 1.
- Post void residual (PVR) in volunteers who micturate or have a mixed catheterization/micturition pattern
- Urine specimen to conduct urinalysis, urine culture and sensitivity, and biomarker evaluation (See Appendix III)
- CBC (Complete Blood Count)
- CMP (Complete Metabolic Panel)
- Pregnancy test - serum (for females only)
- Prostate specific antigen (for males only)
- Urodynamic studies (if not performed 6 months 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 50ml/min. The urodynamic machine will also record the subtracted detrusor pressure (Pdet=Pves – Pabd). Where the Pabd pressure is adjusted at baseline to render Pdet =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 urodynamist 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 [Cipro (generic is permissible) 500 mg 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). <u>If subject has an allergy to Cipro or if urine culture indicates Cipro resistant, another drug may be substituted.</u>

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
- Serum pregnancy test (for females only)
- Urinalysis
- Post void residual in volunteers who micturate or have a mixed catheterization/micturition pattern
- 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 research pharmacist at MEDVAMC.

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.
- 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 (± 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 (± 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.
- Serum pregnancy test (females)
- 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 (± 3 days) post randomization/treatment

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

10.3.4. Visit 6: Week 24 (± 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
- Kidney ultrasound
- 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 access 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 baseline and each study visit. 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 X) 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 deidentify 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 MEDVAMC 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)

Data for all participants enrolled at MEDVAMC will be managed under the privacy guidelines as determined by MEDVAMC.

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. Study data will be kept in a locked file cabinet and/or password protected and encrypted computers and stored on MEDVAMC Drive L.

15.3. Confidentiality

15.3.1 Baylor College of Medicine (BCM) and Michael E. DeBakey Veterans Affairs Medical Center.

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 MEDVAMC Urology Clinic and stored on Drive L.

Regulatory documents will be managed by Research Administration of the Scott Department of Urology, BCM. There will be two actual physical locations, one in the Department's Faculty Center, suite 1610 and the other is 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.

Data for all participant enrolled at MEDVAMC will be managed under the privacy guidelines as determined by MEDVAMC.

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 heart beats 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, and study exit
- Serum pregnancy test for female volunteers of childbearing potential on day of treatment (prior to each treatment)
- 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 MEDVAMC 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

Under Federal Regulations, a VA Medical facility shall provide necessary medical treatment to a research volunteer injured as a result by participation in a research project approved by a VA Research and Development Committee and conducted under the supervision of one or more VA employees. This requirement does not apply to treatment for injuries that result from non-compliance by a research volunteer with study procedures. If an injury as a direct result of study participation is sustained, medical care will be provided by the VA Medical facility. The Department of Veterans Affairs does not normally provide any other form of compensation for injury.

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

Abdel-Meguid TA. Botulinum toxin-A injections into neurogenic overactive bladder--to include or exclude the trigone? A prospective, randomized, controlled trial". J Urol 2010;184:2423-2428. PMID: 20952003

Apostolidis A, Jacques TS, Freeman A, Kalsi V, Popat R, Gonzales G, Datta SN, Ghazi-Noori S, Elneil S, Dasgupta P, Fowler CJ: Histological changes in the urothelium and suburothelium of human overactive bladder following intradetrusor injections of botulinum neurotoxin type A for the treatment of neurogenic or idiopathic detrusor overactivity. Eur Urol. 2008 Jun;53(6):1245-53. Epub 2008 Mar 7.PMID: 18343564

Bennett N, O'Leary M, Patel AS, Xavier M, Erickson JR, Chancellor MB. Can higher doses of oxybutynin improve efficacy in neurogenic bladder? J Urol. 2004 Feb;171(2 Pt 1):749-51. PubMed PMID: 14713802.

Billips BK, Forrestal SG, Rycyk MT, Johnson JR, Klumpp DJ, Schaeffer AJ. Modulation of host innate immune response in the bladder by uropathogenic Escherichia coli". Infect Immun 2007;75:5353-5360. PMID:
17724068 PMCID: PMC2168307

Bhangoo, S., Ren, D., Miller, R. J., Henry, K. J., Lineswala, J., Hamdouchi, C., Li, B., Monahan, P. E., Chan, D. M., Ripsch, M. S. and White, F. A. (2007). Delayed functional expression of neuronal chemokine receptors following focal nerve demyelination in the rat: a mechanism for the development of chronic sensitization of peripheral nociceptors. *Mol Pain* 3, 38. PMID: 18076762 PMCID: 2228278

Blackmer J. Rehabilitation medicine: 1. Autonomic dysreflexia. CMAJ 2003;169:931-935. PMID: 14581313

Bosch JL, Groen J: Neuromodulation: urodynamic effects of sacral (S3) spinal nerve stimulation in patients with detrusor instability or detrusor hyperflexia. Behav Brain Res. 1998 May;92(2):141-50.PMID: 9638956

Bosch JL: Sacral neuromodulation in the treatment of the unstable bladder. Curr Opin Urol. 1998 Jul;8(4):287-91.PMID: 17038970

Bouchelouche K, Alvarez S, Andersen L, Nordling J, Horn T, Bouchelouche P: Monocyte chemoattractant protein-1 production by human detrusor smooth muscle cells. J Urol. 2004 Jan;171(1):462-6.PMID: 14665956

Bouchelouche K, Alvarez S, Horn T, Nordling J, Bouchelouche P: Human detrusor smooth muscle cells release interleukin-6, interleukin-8, and RANTES in response to proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha. Urology. 2006a Jan;67(1):214-9.PMID: 16413378

Bouchelouche, K., Andresen, L., Alvarez, S., Nordling, J., Nielsen, O. H. and Bouchelouche, P. Interleukin-4 and 13 induce the expression and release of monocyte chemoattractant protein 1, interleukin-6 and stem cell factor from human detrusor smooth muscle cells: synergy with interleukin-1beta and tumor necrosis factor-alpha. J Urol 2006b.175, 760-5. PMID:16407046

Coelho A, Dinis P, Pinto R, Gorgal T, Silva C, Silva A, Silva J, Cruz CD, Cruz F, Avelino A. Distribution of the high-affinity binding site and intracellular target of botulinum toxin type A in the human bladder". Eur Urol 2010;57:884-890. PMID: 20044204

De Vivo MJ, Rutt RD, Black KJ et al.: Trends in spinal cord injury demographics and treatment outcome between 1973 and 1986. *Arch Phys Med Rehab* 73:424, 1992. PMID: 1580768
Erickson, D. R., Xie, S. X., Bhavanandan, V. P., Wheeler, M. A., Hurst, R. E., Demers, L. M., Kushner, L., Keay, S. K. (2002). A comparison of multiple urine markers for interstitial cystitis. J Urol 167, 2461-9. PMID: 11992058

Foley SJ, McFarlane JP, Shah PJ: Vesico-ureteric reflux in adult patients with spinal injury. Br J Urol. 1997 Jun;79(6):888-91. PMID: 9202554

Gabella, G. (1999). Structure of the intramural nerves of the rat bladder. J Neurocytol 28, 615-37.PMID: 10851342

Ginsberg D, Gousse A, Keppenne V, Sievert K-D, et.al. Phase 3 Efficacy and Safety Study of Onabotulinumtoxina in Patients with Urinary Incontinence Due to Neurogenic Detrusor Overactivity. J Urol 185:4, Supplement, Page e607, 2011.

Godaly, G., Bergsten, G., Hang, L., Fischer, H., Frendeus, B., Lundstedt, A. C., Samuelsson, M., Samuelsson, P. and Svanborg, C. (2001). Neutrophil recruitment, chemokine receptors, and resistance to mucosal infection. J Leukoc Biol 69, 899-906.PMID: 11404374

Gosselin, R. D., Varela, C., Banisadr, G., Mechighel, P., Rostene, W., Kitabgi, P. and Melik-Parsadaniantz, S. (2005). Constitutive expression of CCR2 chemokine receptor and inhibition by MCP-1/CCL2 of GABA-induced currents in spinal cord neurones. *J Neurochem* 95, 1023-34. PMID: PMID: 16150057

Herschorn S, Gajewski J, Ethans K, Corcos J, Carlson K, Bailly G, Bard R, Valiquette L, Baverstock R, Carr L, Radomski S. Efficacy of botulinum toxin a injection for neurogenic detrusor overactivity and urinary incontinence: a randomized, double-blind trial. J Urol. 2011 Jun;185(6):2229-35. Epub 2011 Apr 16.
PMID: 21497851

Jung, H., Toth, P. T., White, F. A. and Miller, R. J. (2008). Monocyte chemoattractant protein-1 functions as a neuromodulator in dorsal root ganglia neurons. *J Neurochem* 104, 254-63. PMID: 17944871 MCID: PMC2186066

Kaplan SA, Chancellor MB and Blaivas JG: Bladder and sphincter behavior in patients with spinal cord lesions. J Urol 146:113, 1991.PMID: 2056568

Kofoed, K., Schneider, U. V., Scheel, T., Andersen, O. and Eugen-Olsen, J. (2006). Development and validation of a multiplex add-on assay for sepsis biomarkers using xMAP technology. Clin Chem 52, 1284-93.PMID: 16690735

Kronborg CS, Allen J, Vittinghus E, Knudsen UB. Pre-symptomatic increase in urine-orosomucoid excretion in pre-eclamptic women". Acta Obstet Gynecol Scand 2007;86:930-937. PMID: 17653877

Lee J, Barron RL, Patrick D. Qualitative assessment of content validity of the Incontinence Quality of Life Questionnaire (I-QOL) in neurogenic patients (spinal cord injury and MS). Quality of Life Research Vol 14; No 9, pp 2007, Abstract O-4-C05/1488, Nov 2005.

Liu HT, Chancellor MB, Kuo HC. Urinary nerve growth factor levels are elevated in patients with detrusor overactivity and decreased in responders to detrusor botulinum toxin-A injection. *Eur Urol* 2009a, 56(4): 700-706 PMID:18472208

Liu HT, Tyagi P, Chancellor MB, Kuo HC. Urinary nerve growth factor level is increased in patients with interstitial cystitis/bladder pain syndrome and decreased in responders to treatment. BJU Int 2009b;104:1476-1481. PMID: 19522864

Manack A, Motsko SP, Haag-Molkenteller C, Dmochowski RR, Goehring EL Jr, Nguyen-Khoa BA, Jones JK Epidemiology and healthcare utilization of neurogenic bladder patients in a US claims database. Neurourol Urodyn. 2011 Mar;30(3):395-401. doi: 10.1002/nau.21003. Epub 2010 Sep 29. PMID: 20882676

McCullagh P and Nelder JA. 1989. Generalized linear models, London, Chapman and Hall.

McGuire EJ and Brady S: Detrusor-sphincter dyssynergia. J Urol 121:774, 1979. PMID: 458950

Melik-Parsadaniantz, S. and Rostene, W. (2008). Chemokines and neuromodulation. *J Neuroimmunol* 198, 62-8. PMID:18538863

Mengheang, L., J. Hairston, et al. (2011). "1517 Efficacy of Onabotulinumtoxina in Patients with Neurogenic Bladder and Decreased Bladder Compliance." J Urol. 185(4): e608.

Mehta RL. Urine IL-18 levels as a predictor of acute kidney injury in intensive care patients. Nat Clin Pract Nephrol. 2006 May;2(5):252-3. PMID: 16932437.

Mills IW, Drake MJ, Greenland JE, Noble JG, Brading AF: The contribution of cholinergic detrusor excitation in a pig model of bladder hypocompliance. BJU Int. 2000 Sep;86(4):538-43.PMID: 10971288

Mortier, A., Van Damme, J. and Proost, P. (2008). Regulation of chemokine activity by posttranslational modification. Pharmacol Ther.120**,** 197-217 PMID: 18793669

Miyazato M, Sasatomi K, Hiragata S, Sugaya K, Chancellor MB, de Groat WC, Yoshimura N (2008). GABA receptor activation in the lumbosacral spinal cord decreases detrusor overactivity in spinal cord injured rats. J Urol.;179 (3):1178-83. PMID:18206170 PMCID: PMC2744108

Ouslander JG: Management of overactive bladder. N Engl J Med. 2004 Feb 19;350(8):786-99. Review. No abstract available. PMID: 14973214

Paralyzed Veterans of America/Consortium for Spinal Cord Medicine. Acute management of autonomic dysreflexia: individuals with spinal cord injury presenting to health-care facilities. Washington (DC): Paralyzed Veterans of America (PVA); 2001 Jul. 29 p.

Parekattil, S. J., Fisher, H. A. and Kogan, B. A. 2003. Neural network using combined urine nuclear matrix protein-22, monocyte chemoattractant protein-1 and urinary intercellular adhesion molecule-1 to detect bladder cancer. J Urol 169, 917-20. PMID:12576812

Parikh, C. R., Mishra, J., Thiessen-Philbrook, H., Dursun, B., Ma, Q., Kelly, C., Dent, C., Devarajan, P. and Edelstein, C. L. 2006. Urinary IL-18 is an early predictive biomarker of acute kidney injury after cardiac surgery. Kidney Int 70, 199-203. PMID:12576812

Patrick DL, Martin ML, Bushnell DM, Yalcin I, Wagner TH, Buesching DP: Quality of life of women with urinary incontinence: further development of the incontinence quality of life instrument (I-QOL). Urology. 1999 Jan;53(1):71-6. Erratum in: Urology 1999 May;53(5):1072. PMID: 9886591

Pirtskalaishvili, G., Getzenberg, R. H. and Konety, B. R. (1999). Use of urine-based markers for detection and monitoring of bladder cancer. Tech Urol 5, 179-84. PMID: 10591254

Qin, X., Wan, Y. and Wang, X. (2005). CCL2 and CXCL1 trigger calcitonin gene-related peptide release by exciting primary nociceptive neurons. J Neurosci Res 82, 51-62.PMID: 16047385

Rovin, B. H., Song, H., Birmingham, D. J., Hebert, L. A., Yu, C. Y. and Nagaraja, H. N. 2005. Urine chemokines as biomarkers of human systemic lupus erythematosus activity. J Am Soc Nephrol 16, 467-73.
PMID:15601744

Sadeghi, M., Daniel, V., Naujokat, C., Weimer, R. and Opelz, G. 2005. Strikingly higher interleukin (IL)-1alpha, IL-1beta and soluble interleukin-1 receptor antagonist (sIL-1RA) but similar IL-2, sIL-2R, IL-3, IL-4, IL-6, sIL-6R, IL-10, tumour necrosis factor (TNF)-alpha, transforming growth factor (TGF)-beta and interferon IFN-gamma urine levels in healthy females compared to healthy males: protection against urinary tract injury? Clin Exp Immunol 142, 312-7. PMID:16232218 PMCID: PMC1809507

Schurch B, de Sèze M, Denys P, Chartier-Kastler E, Haab F, Everaert K, Plante P, Perrouin-Verbe B, Kumar C, Fraczek S, Brin MF; Botox Detrusor Hyperreflexia Study Team. Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. J Urol. 2005 Jul;174(1):196-200. PubMed PMID:15947626.

Schurch B, Stöhrer M, Kramer G, Schmid DM, Gaul G, Hauri D. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol. 2000 Sep;164 (3Pt 1):692-7. PMID: 10953127

Segerer, S. and Nelson, P. J. 2005. Chemokines in renal diseases. ScientificWorldJournal 5,835-44. PMID:
16200331

Smith CP, Nishiguchi J, O'Leary M, Yoshimura N, Chancellor MB. Single-institution experience in 110 patients with botulinum toxin A injection into bladder or urethra". Urology 2005;65:37-41. PMID. 15667859

Stöhrer M, Mürtz G, Kramer G, Schnabel F, Arnold EP, Wyndaele JJ; Propiverine Investigator Group : Propiverine compared to oxybutynin in neurogenic detrusor overactivity--results of a

randomized, double-blind, multicenter clinical study. Eur Urol. 2007 Jan;51(1):235-42. Epub 2006 May 2. PMID: 16698176

Torrence AE, Brabb T, Viney JL, Bielefeldt-Ohmann H, Treuting P, Seamons A, Drivdahl R, Zeng W, Maggio-Price L. Serum biomarkers in a mouse model of bacterial-induced inflammatory bowel disease". Inflamm Bowel Dis Inflamm Bowel Dis. 2008 Apr;14(4):480-90. PMID: 18095317

Tyagi P, Barclay D, Zamora R, Yoshimura N, Peters K, Vodovotz Y, Chancellor M. Urine Cytokines Suggest an Inflammatory Response in the Overactive Bladder: a Pilot Study". Int Urol Nephrol 2009a. PMID: 19784793

Tyagi P, Tyagi V, Yoshimura N, Witteemer E, Barclay D, Loughran P, Zamora R, Vodovotz Y. 2009. Gender-Based Reciprocal Expression of Transforming Growth Factor-b1 and the Inducible Nitric Oxide Synthase in a Rat Model of Cyclophosphamide-Induced Cystitis J Inflamm. 2009b Aug 19;6:23, PMID: 19691848

Yalla SV, Blunt KJ, Fam BA et al.: Detrusor-urethral sphincter dyssynergia. J Urol 118:1026, 1977. PMID: 926242

Yoshimura N, Bennett NE, Hayashi Y, Ogawa T, Nishizawa O, Chancellor MB, de Groat WC, Seki S. Bladder overactivity and hyperexcitability of bladder afferent neurons after intrathecal delivery of nerve growth factor in rats". J Neurosci 2006;26:10847-10855. PMID: 17050722

Yuridullah R, Corrow KA, Malley SE, Vizzard MA. Expression of fractalkine and fractalkine receptor in urinary bladder after cyclophosphamide (CYP)-induced cystitis". Auton Neurosci 2006;126-127:380-389. PMID:
16651033 PMCID: PMC1475778

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 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
Post void residual	X	X		X	X	X
Kidney ultrasound within 6 months	X					X
Urodynamic studies within 6 months and off meds for 2 weeks prior to urodynamic studies	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
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
Patient Global Assessment				X	X	X
Adverse event assessments		X	X	X	X	X
Subject stipend for transportation		X		X	X	X

Non-standard of care is highlighted in yellow.

APPENDIX II

URINE COLLECTION PROTOCOL

OnaBoNT-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 Drs. Chancellor and Tyagi's lab when a set of urine specimens from a batch of 10 patients is complete:

1. 50ml of undiluted urine collected preferably from volunteers when they feel a full sensation or the need to catheterize will be used for analysis.
2. Date and time of collection will be recorded.
3. Collection should immediately be placed on ice to halt enzymatic activity.
4. Specimens will be centrifuged for 10 minutes at 5,000x g within 30 to 60 minutes to remove cells from urine as sediment.
5. Supernatant will be 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. If the -80°C freezer is not immediately available, the urine supernatant can be stored at 4°C for 16h and room temperature for 6 hours.
6. Ship OVERNIGHT with AM delivery in sufficient **DRY ICE** to:

Urology Laboratory
Department of Urology
William Beaumont Hospital Research Institute
3811 West 13 Mile Road
Royal Oak, MI 48073
(248) 551-8296

URINE SAMPLE ACQUISITION FORM

(to be filled and submitted with each sample)

H #: 26292

Subject ID#: _____

Date of collection: _____

Time of collection: _____

Time samples were frozen: _____

Were specimens centrifuged at 5,000xg for 10 minutes within 30 to 60 minutes? □ No □ Yes

Were the supernatant removed and divided into 1.5 ml aliquots? □ No □ Yes

Were the aliquots

immediately placed in -80°C freezer? □ No □ Yes

maintained at 4 °C until transported within 16 hours to -80°C freezer □ No □ Yes

how many hours and minutes before placing in -80°C freezer ____hours ___minutes

stored at room temperature for up to 6 hours until transported to -80°C freezer □ No □ Yes

how many hours and minutes before placing in -80°C freezer ____hours _____minutes

Did any samples ever thaw after freezing?

□ No □ Yes

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

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

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

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

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

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

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

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

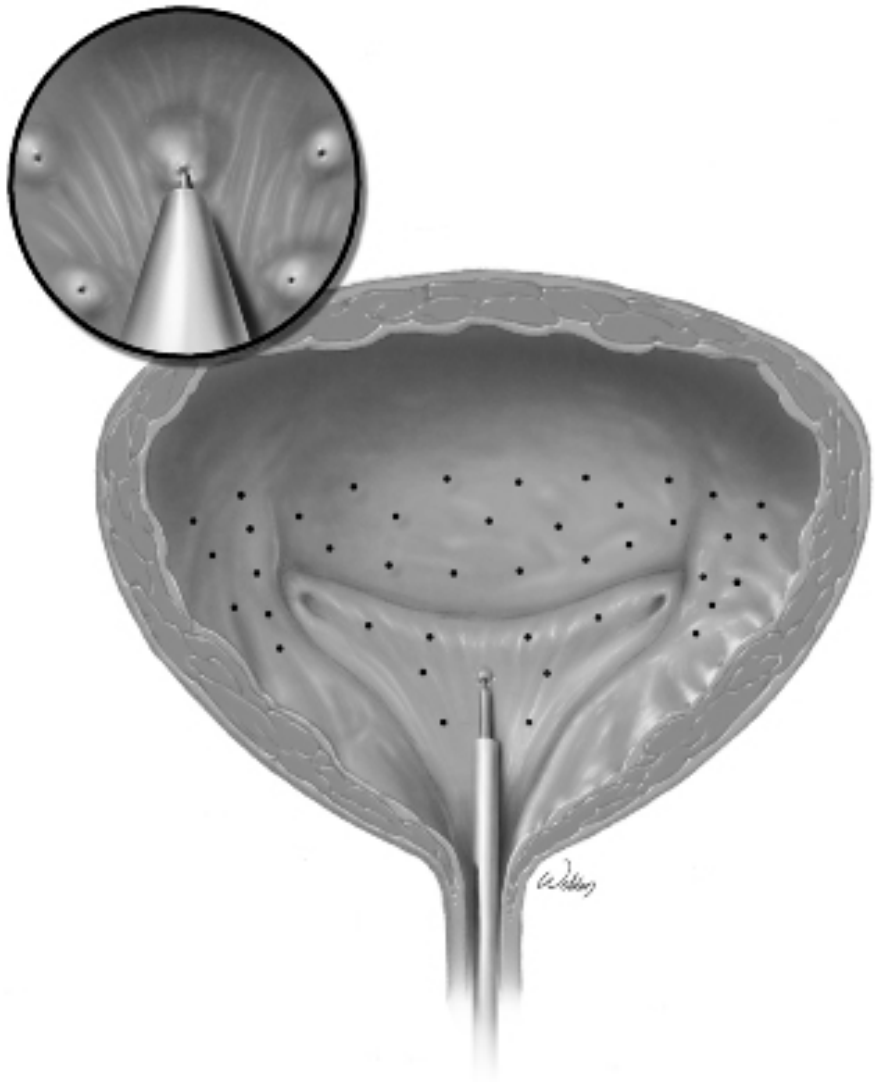
APPENDICES IV

QUESTIONNAIRES

APPENDIX V

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 detrusorvia 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.

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

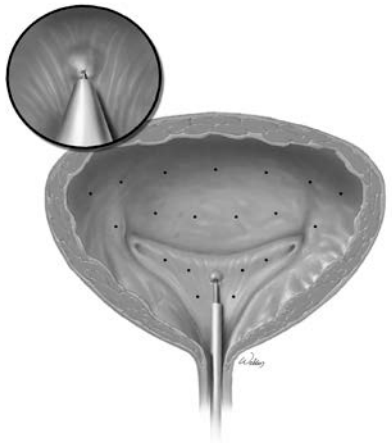
PI: Christopher P. Smith, MD **Org:** Baylor College of Medicine **Award Amount:** 904,516.00

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. IRB/VA approvals for advertising were approved. BCM IRB has approved the TIRR Memorial Hermann site. The sub-award is being finalized and enrollment will begin as soon as possible after HPRO approval is received.



BOTOX Injection Pattern Diagram

Accomplishment: Chart review for eligibility continues. Out of 131 MEDVAMC charts reviewed, no patients met eligibility or agreed to participate.

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

Updated: October 2015

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: $200,000

Actual Expenditure: $198,470

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 – July 8, 2015
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 VA**	**BCM TIRR**	**WBH**
Major Task 1: Submit regulatory documents and obtain approval for study start				
Subtask 1: IRB applications will be submitted	1-2	CPS		
Subtask 2: VA applications will be submitted	1-3	CPS		
Subtask 3: TIRR Research committee application submitted	36		CPS	
Milestone Achieved: Local IRB (VA) approval; (TIRR) approval*	(2) (34)			
Milestone Achieved: MEDVAMC ACOS approval	3			
*Milestone Achieved: HRPO** approval*	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	CPS/ST	
Milestone Achieved: 1st participant consented (Lost to Follow-up)	14			
Subtask 2: Enrollment to be performed	6 - 42	CPS/ST	CPS/ST	
Subtask 3: All treatment and follow up to be performed	6 - 52	CPS/ST	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	CPS	
Subtask 2: Final analysis will be completed	36 - 54	CPS	CPS	
Subtask 3: Publications developed	54 - 60	CPS	CPS	MBC

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)

Projected Quarterly Enrollment

	Year 1				Year 2				Total
Target Enrollment Pilot Study (#1) (per quarter)* **	**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**

	Year 3				Year 4				Year 5 (No Cost Extension)				Total
Target Enrollment Pilot Study (#1) (per quarter)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	
BCM (VA)	0	0	0	0	0	0	0	0	0	0	0	0	0
BCM (TIRR)	0	0	0	0	0	0	0	0	0	0	0	0	0
Target Enrollment (cumulative)	**0**	**0**	**6**	**6**	**6**	**6**	**6**	**6**	**0**	**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.*