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

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PREPARED FOR: U.S. Army Medical Research and Materiel Command

Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The purpose is to evaluate the safety and efficacy of 200 U OnaBoNT-A injected into the detrusor versus oral oxybutynin for the treatment of urinary incontinence (UI) caused by neurogenic detrusor overactivity (NDO) in spinal cord injured volunteers; and (2) To determine the potential role of urine biomarkers as patient selection and surrogate endpoints of treatment outcome predictors. Thirty-six patients will be randomized to two treatment groups.

The first patient was enrolled to the study at The Institute of Rehabilitation and Research (TIRR) on June 17, 2016. A total of thirteen patients have been consented to date at TIRR. Three have completed the study. Three are continuing on protocol with each having been injected with the study drug. Enrollment is continuing.

The study was closed at the Michael E. DeBakey Veterans Affairs Medical Center – Houston in July 2016 due to lack of accrual.

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

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	11	19b. TELEPHONE NUMBER *(include area code)*

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1. **INTRODUCTION:**
   - This purpose of this clinical research study is to evaluate the benefits of 200 Units (U) onabotulinum toxinA (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 patients. 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 endpoint of treatment outcome predictors.

2. **KEYWORDS:**
   - Botulinum Toxin
   - Oxybutynin
   - Overactive Bladder
   - Spinal Cord Injury
   - Urinary Incontinence
   - Nerve Growth Factor
   - Urine Biomarkers

3. **ACCOMPLISHMENTS:**
   - **What were the major goals of the project?**
     - Aim 1: Screen, enroll, and treat 36 patients randomized to two treatment groups at two sites
       - Volunteers will be randomized according to a block randomization approach designed by the statistician and implemented by the MEDVAMC Research Pharmacy: ARM 1: These patients will receive onaBoNT-A 200 U bladder injection and placebo oral capsule daily or ARM 2: These patients will receive saline bladder injections 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. Patients will be followed for 26 weeks post treatment 1.
       - Begin enrollment within 6 months after receiving grant.
       - Enrollment to be performed months 6-36
       - All treatment and follow up to be performed months 6-42

     - Aim 2: Evaluation of biomarkers pretreatment and during follow up
       - Urinary NGF and chemokine/cytokine levels will be measured prior to treatment 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 and shipped to the Urology Research laboratory at William Beaumont Hospital, Royal Oak, MI for analysis of nerve growth factor (NGF) and urinary chemokines/cytokines.
       - All biomarker analysis to be conducted months 6-42
   - **What was accomplished under these goals?**
     - Aim 1:
       - Michael DeBakey Veterans Affairs Medical Center – Houston
         - This study was conducted at this site from initial study opening in 2013 to closure in July 2016. One patient signed an informed consent document but then was never in contact again. After numerus attempts to contact him, he was withdrawn from the study.
         - Over the course of the study at MEDVAMC-Houston, 257 patient letters were mailed and 1,379 charts were reviewed. No additional subjects signed consent forms.
       - TIRR (The Institute of Rehabilitation and Research) Memorial Hermann

- The first subject was enrolled at TIRR in July 2016 with an additional 12 being enrolled. Five subjects completed the study. Four subjects were screen failures. Two were withdrawn due to non-compliance of visit appointments. One subject was incarcerated; therefore, unable to attend the scheduled appointments. One withdrew due to an unrelated medical condition.
- Over the course of the study at TIRR, 1,209 charts were reviewed.

RESULTS

Questionnaire Data

IQOL (Mean change from baseline to 4 wks post-treatment, positive score is improvement)

Oxybutynin (4 pts)	14
Botulinum Toxin (2 pts)	14

IQOL-N (Mean change from baseline to 4 wks post-treatment, positive score is improvement)

Oxybutynin (4 pts)	3.5
Botulinum Toxin (2 pts)	2.5

OAB-PTSQ (Mean change from baseline to 4 wks post-treatment, positive score is improvement; 0 = no progress, 1 = some progress, 2 = moderate progress)

Oxybutynin (4 pts)	0.833
Botulinum Toxin (2 pts)	2

PGA (Patient Global Assessment, mean change from baseline to 4 wks post-treatment; 0= no change; 1 = almost the same; 2 = little better; 3 = somewhat better; 4 = moderately better)

IQOL	Question #1	Question #2	Question #3	Question #4
Oxybutynin (4 pts)	3.25	1.75	1.75	0.75
Botulinum Toxin (2 pts)	4	3.5	3.5	3.5

Voiding Diary Data

(Mean change in # of daily leakage episodes from baseline to 12 wk followup; 1 = mild leakage; 2 = moderate leakage; 3 = severe leakage)

	1	2	3
Oxybutynin (3 pts)	3.33	-2.67	-11.67
Botulinum Toxin (2 pts)	-2.5	1.5	-3

Urodynamic Data

	Oxybutynin (4 patients)	Botulinum Toxin (2 patients)
Mean change 1st IDC	+11ml	+96ml
Mean change Max Bladder Capacity	-118 ml	+212 ml

Conclusions: Due to small patient accrual it is impossible to make any statements of significance. For the most part, little to no difference was seen between both

groups regarding questionnaire, voiding diary and urodynamic data. The oxybutynin group appeared to show more improvement in severe incontinence than the botulinum toxin group when looking at voiding diary data. On the other hand, the botulinum toxin treated group subjectively improved more from treatment based on Patient Global Assessment and OAB-PTSQ data. In addition, patients injected with botulinum toxin appear to show a marked improvement in bladder capacity and increase in volume of 1st involuntary detrusor contraction compared to patients given oral oxybutynin. The success of botulinum toxin treatment was largely driven by a marked improvement in subjective and objective parameters noted in 1 of 2 patients injected with botulinum toxin.

- **Aim 2:**
  - **Biomarkers Report (Dr. Michael Chancellor, Beaumont Hospital)**

    - Sample Populations: The analysis at Beaumont used urine samples shipped from Baylor that had a preservative (Norgen Biotek) added immediately after collection.

      The study had approval from Beaumont Health System's Institutional Review Board (IRB). Samples were provided to the Beaumont team with only subject ID numbers and the Beaumont team was blinded to treatment randomized throughout the analysis. Only after data were send to Baylor were subject code released to the Beaumont team.
    - Dataset: The urine samples send from Baylor to Beaumont included 6 subjects. Subjects 101, 103, 107, 110, 111, and 112. Samples were sent from visits 2, 4, 5, and 6 but there was no collection from 4 of the 24 planned collection data points.

    - Measurement of Cytokines in Urine Samples: Expression of NGF and MMP-9 were analyzed by commercially available ELISA kits for the specific protein. Protein concentrations used were the average of technical duplicates. Each plate was run with a standard curve and two quality controls to qualify assay performance.

RESULTS

Sample size of only 4 oxybutynin and 2 botulinum toxin were too small for statistical analysis. Descriptive analysis noted no observational differences in the 2 toxin subjects vs the 4 oxybutynin treated subjects. But there were not enough data points for proper analysis.

NGF was less than 10pg/mL, the minimal detection limit, in all the samples. The NGF peptide standards provided by the manufacturer, other urine samples containing NGF, and the ELISA kit functioned satisfactorily. Thus, NGF is not a good candidate biomarker for this population of patients using preserved urine collection methods.

Table 1. DoD samples

Patient ID	Treatment
101	saline/oxybutynin
103	saline/oxybutynin
107	Botox/placebo
110	saline/oxybutynin
111	Botox/placebo
112	saline/oxybutynin

Table 2. MMP9 urinary concentrations (pg/mL) at the 4 visit time points.

Patient	V2	V4	V5	V6
101	640.377	907.385	7696.011	8524.71
103	0	241.387	28.691	98.59
107	7558.177		7981.771	8031.609
110	4630.614	55.847	3594.146	
111	2104.902		1452.513	2869.88
112	8079.788		5678.395	6943.471

Figure 1. Standard Curve MMP-9 ELISA

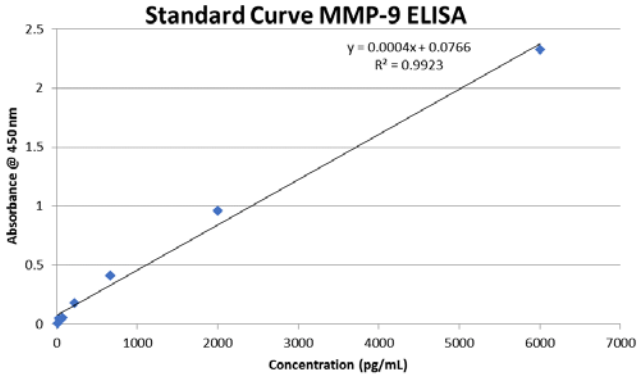
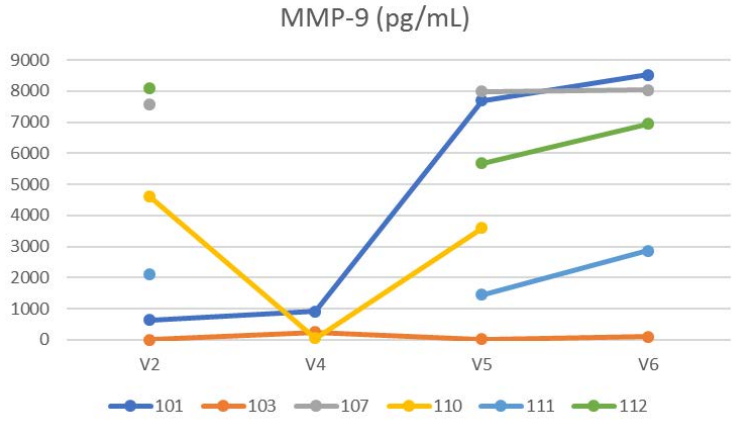


Figure 2. MMP-9 Results Plot



Conclusion: There were no observable differences in urine proteins between oxybutynin treatment or botulinum treated subjects but the sample size was too small for statistical calculation. Larger study size would be required for biomarker analysis. There were no complications or study violations at Beaumont in the analysis of urine biomarker. All samples will be disposed of in accordance to approved protocol at end of the study.

- **What opportunities for training and professional development has the project provided?**
  - This project allowed the PI and research coordinator to interact with multidisciplinary teams at the MEDVAMC and TIRR as well as with the bioresearch team at Beaumont Hospital.
  - Nothing to report

- **How were the results disseminated to communities of interest?**
  - The data set was too small to report to the scientific community in a formalized setting.
  - Nothing to report

- **What do you plan to do during the next reporting period to accomplish the goals?**
  - Nothing to Report

4. **IMPACT:**
   - **What was the impact on the development of the principal discipline(s) of the project?**
     - The data set is too small to make scientific recommendations. Qualitatively, it appears that the botulinum toxin treated group demonstrated greater improvements in urodynamic parameters.

   - **What was the impact on other disciplines?**
     - Our referral partners in Physical Medicine and Rehabilitation are more comfortable and likely to refer neurogenic bladder patients for botulinum toxin treatment.

   - **What was the impact on technology transfer?**
     - Nothing to report

   - **What was the impact on society beyond science and technology?**
     - Increased awareness of botulinum toxin as a therapeutic agent for neurogenic bladder patients who fail or are intolerant to oral medications.

5. **CHANGES/PROBLEMS:**
   - **Changes in approach and reasons for change**
     - Nothing to Report
   - **Actual or anticipated problems or delays and actions or plans to resolve them**
     - Continued poor accrual based on availability of botulinum toxin as a commercially available therapeutic agent led to decision to close the study.
   - **Changes that had a significant impact on expenditures**
     - Nothing to report
   - **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
     - Nothing to report
   - **Significant changes in use or care of human subjects**
     - Nothing to report
   - **Significant changes in use or care of vertebrate animals.**
     - Nothing to report
   - **Significant changes in use of biohazards and/or select agents**
     - Nothing to report

6. **PRODUCTS:**
   - **Publications, conference papers, and presentations**
     - Nothing to report: only 6 patients finished the study and the data set was too limited to make scientific conclusions.
   - **Journal publications.**
     - Nothing to report
   - **Books or other non-periodical, one-time publications.**
     - Nothing to report
   - **Other publications, conference papers, and presentations.**
     - Nothing to report
   - **Website(s) or other Internet site(s)**
     - Nothing to report
   - **Technologies or techniques**
     - Nothing to report
   - **Inventions, patent applications, and/or licenses**
     - Nothing to report
   - **Other Products**
     - Nothing to report

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**
   - **What individuals have worked on the project?**

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Name:	*Christopher P. Smith, MD, MBA, MMS*
Project Role:	*PI*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1.2
Contribution to Project:	
Funding Support:	

Name:	*Michael B. Chancellor, MD*
Project Role:	*Co-Investor*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*0.6*
Contribution to Project:	*Oversight of biomarkers testing*
Funding Support:	

Name:	Pradeep Tyagi, PhD
Project Role:	Co-Investor
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	0.6
Contribution to Project:	Oversight of biomarkers testing
Funding Support:	

Name:	*Sebrina Tello, CCRP*
Project Role:	*Study Coordinator*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*4.8*
Contribution to Project:	*Ms. Tello performed the study coordination.*
Funding Support:	

Name:	*Linda C. Higgins, CCRP*
Project Role:	*Regulatory affairs coordination*
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	*2.4*
Contribution to Project:	*Ms. Higgins performed all communications with the BCM IRB and all affiliated institutions' committees, as well, as the HRPO and DOD communications.*
Funding Support:	

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  - Nothing to Report

- **What other organizations were involved as partners?**

- **Organization Name:** Baylor College of Medicine
- Location of Organization: Houston, TX
- Partner's contribution to the project IRB of Record for Michael E. DeBakey Veterans Affairs Medical Center – Houston (MEDVAMC) and The Institute of Rehabilitation and Research (TIRR)
- Financial support: N/A
- In-kind support*:* N/A
- Facilities: N/A
- Collaboration: N/A
- Personnel exchanges: N/A and
- Other: N/A

- **Organization Name:** Michael E. DeBakey Veterans Affairs Medical Center – Houston (MEDVAMC)
- Location of Organization: Houston, TX
- Partner's contribution to the project
- Financial support: N/A
- In-kind support: *Software, computers, equipment, etc., available to project staff;*
- Facilities: Clinic space to see research subjects
- Collaboration: N/A
- Personnel exchanges*:* N/A
- Other: N/A

- **Organization Name:** The Institute of Rehabilitation and Research (TIRR)
- Location of Organization: Houston, TX
- Partner's contribution to the project
- Financial support: N/A
- In-kind support: *Software, computers, equipment, etc., available to project staff;*
- Facilities: Clinic space to see research subjects
- Collaboration: N/A
- Personnel exchanges*:* N/A
- Other: N/A

- **Organization Name:** Beaumont Research Institute
- Location of Organization: Royal Oak, MI
- Partner's contribution to the project:
- Financial support: N/A
- In-kind support: *Software, computers, equipment, etc., available to project staff;*
- Facilities: Research laboratory space for testing of specimens.
- Collaboration: N/A
- Personnel exchanges*:* N/A
- Other: N/A

8. **APPENDICES:**
   - BCM IRB Study Closure Acknowledgment
   - Questionnaires
     - Incontinence Quality of Life Instrument
     - I-QOL Neurogenic Module
     - OAB-Patient Satisfaction With Treatment Questionnaire (OAB-PSTQ)
     - Patient Global Assessment

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MEMORANDUM

TO: CHRISTOPHER PATRICK SMITH
UROLOGY

FROM: BAMBI JO GRILLEY, B.S.
Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals

DATE: June 26, 2018

RE: **H-34972 - A DOUBLE-BLIND, RANDOMIZED STUDY OF THE SAFETY AND EFFICACY OF ONABOTULINUMTOXINA (ONABONT-A) VERSUS ORAL OXYBUTYNIN IN SPINAL CORD INJURED PATIENTS WITH NEUROGENIC DETRUSOR OVERACTIVITY (PROTOCOL NUMBER 11-09-10-04) (TIRR)**

Your request that the above referenced protocol be closed, has been noted and filed with the protocol.

You can access any document related to this closed study via the BRAIN database at any time.

Synopsis:
The enrollment for this study has been difficult and the DOD expiration date is September 2018. Thirteen patients signed consent forms. Four completed the study,11 were screen failures, and 2 were withdrawn.

INCONTINENCE QUALITY OF LIFE INSTRUMENT (I-QOL)

PLEASE READ THIS CARFEULLY

ON THE FOLLOWING PAGES YOU WILL FIND SOME STATEMENTS THAT HAVE BEEN MADE BY PEOPLE WHO HAVE URINARY INCONTINENCT (LEAKING URINE WHEN YOU DON'T WANT TO).

PLEASE CHOOSE THE RESPONSE THAT APPLIES BEST TO YOU RIGHT NOW AND CIRCLE THE NUMBER OF YOUR ANSWER.

IF YOU ARE UNSURE ABOUT HOW TO ANSWER A QUESTION, PLEASE GIVE THE BEST ANSWER YOU CAN.

THERE ARE NO RIGHT OR WRONG ANSWERS.

YOUR ANSWERS WILL BE KEPT STRICTLY

Incontinence Quality Of Life

Your Feelings

(Please circle the number of your answer.)

1. I worry about not being able to get to the toilet on time.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

2. I worry about coughing or sneezing because of my urinary problems or incontinence.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

3. I have to be careful standing up after I've been sitting down because of my urinary problems or incontinence.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

Continued on next page

(Please circle the number of your answer.)

4. I worry about where toilets are in new places.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

5. I feel depressed because of my urinary problems or incontinence.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

6. Because of my urinary problems or incontinence, I don't feel free to leave my home for long periods of time.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

Continued on next page

(Please circle the number of your answer.)

7. I feel frustrated because my urinary problems or incontinence prevents me from doing what I want.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

8. I worry about others smelling urine on me.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

9. My urinary problems or incontinence is always on my mine.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

Continued on next page

(Please circle the number of your answer.)

10. It's important for me to make frequent trips to the toilet.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

11. Because of my urinary problems or incontinence, it's important to plan every detail in advance.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

12. I worry about my urinary problems or incontinence getting worse as I grow older.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

Continued on next page

(Please circle the number of your answer.)

13. I have a hard time getting a good night of sleep because of my urinary problems or incontinence.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

14. I worry about being embarrassed or humiliated because of my urinary problems or incontinence.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

15. My urinary problems or incontinence makes me feel like I'm not a healthy person.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

Continued on next page

(Please circle the number of your answer.)

16. My urinary problems or incontinence makes me feel helpless.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

17. I get less enjoyment out of life because of my urinary problems or incontinence.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

18. I worry about wetting myself.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

Continued on next page

(Please circle the number of your answer.)

19. I feel like I have no control over my bladder.

1. EXTREMELY
2. QUITE A BIT
3. MODERATELY
4. A LITTLE
5. NOT AT ALL

20. I have to watch what or how much I drink because of my urinary problems or incontinence.

1. EXTREMELY
2. QUITE A BIT
3. MODERATELY
4. A LITTLE
5. NOT AT ALL

21. My urinary problems or incontinence limit my choice of clothing.

1. EXTREMELY
2. QUITE A BIT
3. MODERATELY
4. A LITTLE
5. NOT AT ALL

Continued on next page

(Please circle the number of your answer.)

22. I worry about having sex because of my urinary problems or incontinence.

1. EXTREMELY
2. QUITE A BIT
3. MODERATELY
4. A LITTLE
5. NOT AT ALL

END OF QUESTIONNAIRE

THANK YOU FOR YOUR RESPONSES

Incontinence Quality of Life Instrument Neurogenic Module

PLEASE READ THIS CARFEULLY

PLEASE CHOOSE THE RESPONSE THAT APPLIES BEST TO YOU RIGHT NOW AND CIRCLE THE NUMBER OF YOUR ANSWER.

IF YOU ARE UNSURE ABOUT HOW TO ANSWER A QUESTION, PLEASE GIVE THE BEST ANSWER YOU CAN.

THERE ARE NO RIGHT OR WRONG ANSWERS.

YOUR ANSWERS WILL BE KEPT STRICTLY

Incontinence Quality Of Life Neurogenic Module

(Please circle the number of your answer.)

1. I have to limit caffeine drinks or alcohol because of my urinary problems or incontinence.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

2. I worry about the long-term effect of catheterizations on my urinary tract infections or other health problems.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

3. Accessibility and privacy in public toilets are important to me.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

Continued on next page

(Please circle the number of your answer.)

4. It bothers me to have to catheterize on a regular schedule.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

5. It bothers me to have to use incontinence pads or diapers.

    1. EXTREMELY
    2. QUITE A BIT
    3. MODERATELY
    4. A LITTLE
    5. NOT AT ALL

END OF QUESTIONNAIRE

THANK YOU FOR YOUR RESPONSES

OAB-PATIENT SATISFACTION WITH TREATMENT QUESTIONNAIRE (OAB_PSTQ)

Please answer each questions by checking the box which best describes your situation.

All answers are kept

Answers should come from your alone, not family, friends, or the doctor's staff.

1. In the past 4 weeks, how satisfied have you been overall with your current or recent treatment(s)

   ☐ Very Satisfied

   ☐ Somewhat Satisfied

   ☐ Neutral

   ☐ Somewhat Dissatisfied

   ☐ Very Dissatisfied

   ☐ Does not apply to me

2. In the past 4 weeks, how satisfied have you been during your treatment's effect on how frequently you have to urinate during the **day**?

   ☐ Very Satisfied

   ☐ Somewhat Satisfied

   ☐ Neutral

   ☐ Somewhat Dissatisfied

   ☐ Very Dissatisfied

   ☐ Does not apply to me

Continued on next page

(Please place a check (√) by your answer.)

3. In the past 4 weeks, how satisfied have you been during your treatment's effect on how frequently you have to urinate during the **night**?

   ☐ Very Satisfied

   ☐ Somewhat Satisfied

   ☐ Neutral

   ☐ Somewhat Dissatisfied

   ☐ Very Dissatisfied

   ☐ Does not apply to me

4. In the past 4 weeks, how satisfied have you been during your treatment's effect on how frequently you have 'wetting accidents' due to **laughing, coughing, sneezing, or physical exercise**?

   ☐ Very Satisfied

   ☐ Somewhat Satisfied

   ☐ Neutral

   ☐ Somewhat Dissatisfied

   ☐ Very Dissatisfied

   ☐ Does not apply to me

5. In the past 4 weeks, how satisfied have you been during your treatment's effect on the uncontrollable urge to urinate?

   ☐ Very Satisfied

   ☐ Somewhat Satisfied

   ☐ Neutral

   ☐ Somewhat Dissatisfied

   ☐ Very Dissatisfied

   ☐ Does not apply to me

Continued on next page

(Please place a check (√) by your answer.)

6. In the past 4 weeks, how satisfied have you been during your treatment's effect on your ability to freely engage in social, work, or leisure activities with confidence (e.g., sports, hobbies, shopping, etc.)?

   ☐ Very Satisfied

   ☐ Somewhat Satisfied

   ☐ Neutral

   ☐ Somewhat Dissatisfied

   ☐ Very Dissatisfied

   ☐ Does not apply to me

7. In the past 4 weeks, how satisfied have you been during your treatment's effect on your enjoyment of life?

   ☐ Very Satisfied

   ☐ Somewhat Satisfied

   ☐ Neutral

   ☐ Somewhat Dissatisfied

   ☐ Very Dissatisfied

   ☐ Does not apply to me

8. In the past 4 weeks, how satisfied have you been during your treatment's effect on reducing fatigue and sleep interruptions?

   ☐ Very Satisfied

   ☐ Somewhat Satisfied

   ☐ Neutral

   ☐ Somewhat Dissatisfied

   ☐ Very Dissatisfied

   ☐ Does not apply to me

Continued on next page

(Please place a check (√) by your answer.)

9. In the past 4 weeks, how satisfied have you been during your treatment's effect on your travel?

- ☐ Very Satisfied
- ☐ Somewhat Satisfied
- ☐ Neutral
- ☐ Somewhat Dissatisfied
- ☐ Very Dissatisfied
- ☐ Does not apply to me

10. In the past 4 weeks, how satisfied have you been during your treatment's effect on your relationships with loved ones?

- ☐ Very Satisfied
- ☐ Somewhat Satisfied
- ☐ Neutral
- ☐ Somewhat Dissatisfied
- ☐ Very Dissatisfied
- ☐ Does not apply to me

11. In the past 4 weeks, how satisfied have you been during your treatment's effect on your ability to engage in sexual activity?

- ☐ Very Satisfied
- ☐ Somewhat Satisfied
- ☐ Neutral
- ☐ Somewhat Dissatisfied
- ☐ Very Dissatisfied
- ☐ Does not apply to me

Continued on next page

(Please place a check (√) by your answer.)

12. In the past 4 weeks, how satisfied have you been with the amount of money you spent on treatment(s) for overactive bladder or urinary incontinence?

- ☐ Very Satisfied
- ☐ Somewhat Satisfied
- ☐ Neutral
- ☐ Somewhat Dissatisfied
- ☐ Very Dissatisfied
- ☐ Does not apply to me

13. In the past 4 weeks, how satisfied have you been during your treatment's ability to reduce your embarrassment due to your overactive bladder or urinary incontinence?

- ☐ Very Satisfied
- ☐ Somewhat Satisfied
- ☐ Neutral
- ☐ Somewhat Dissatisfied
- ☐ Very Dissatisfied
- ☐ Does not apply to me

14. In the past 4 weeks, how would you rate the side effects due to your treatment(s)?

- ☐ No Side Effects
- ☐ Mild Side Effects
- ☐ Moderate Side Effects
- ☐ Severe Side Effects

Continued on next page

Question 15 should only be answered at the DAY 1 visit PRIOR to the administration of the study medication.

15. Please list your top 1 or 2 primary goal(s) (top 1 or 2 only) for treatment of your overactive bladder.

1. _____

2. _____

Question 16 should only be answered at follow-up visits AFTER the study drug administration.

16. Looking back at our primary goal(s) for treatment, how would you rate how effectively the treatment helped you achieve your stated goals?

Goal 1:

☐ No Progress in Achieving this Goal

☐ Some Progress in Achieving this Goal

☐ Moderate Progress in Achieving this Goal

☐ Significant Progress in Achieving this Goal

☐ Complete Achievement of this Goal.

Goal 2 (if listed at baseline):

☐ No Progress in Achieving this Goal

☐ Some Progress in Achieving this Goal

☐ Moderate Progress in Achieving this Goal

☐ Significant Progress in Achieving this Goal

☐ Complete Achievement of this Goal.

Thank you. You have completed this questionnaire!

PATIENT GLOBAL ASSESSMENT (PGA)

1. Since your last clinic visit, has there been any change in your overall symptoms related to your overactive bladder problems?

Place "X" next to the statement that most accurately reflects your opinion:

_____	-7	A very great deal worse
_____	-6	A great deal worse
_____	-5	A good deal worse
_____	-4	Moderately worse
_____	-3	Somewhat worse
_____	-2	A little worse
_____	-1	Almost the same, hardly any worse at all
_____	0	No change
_____	1	Almost the same, hardly any better at all
_____	2	A little better
_____	3	Somewhat better
_____	4	Moderately better
_____	5	A good deal better
_____	6	A great deal better
_____	7	A very great deal better

Continued on next page

1. Since your last clinic visit, has there been any change in your overall quality of life related to your overactive bladder problems?

Place "X" next to the statement that most accurately reflects your opinion:

_____	-7	A very great deal worse
_____	-6	A great deal worse
_____	-5	A good deal worse
_____	-4	Moderately worse
_____	-3	Somewhat worse
_____	-2	A little worse
_____	-1	Almost the same, hardly any worse at all
_____	0	No change
_____	1	Almost the same, hardly any better at all
_____	2	A little better
_____	3	Somewhat better
_____	4	Moderately better
_____	5	A good deal better
_____	6	A great deal better
_____	7	A very great deal better

Continued on next page

3. Since your last clinic visit, has there been any change in your activity limitations related to your overactive bladder problems?

Place "X" next to the statement that most accurately reflects your opinion:

_____	-7	A very great deal worse
_____	-6	A great deal worse
_____	-5	A good deal worse
_____	-4	Moderately worse
_____	-3	Somewhat worse
_____	-2	A little worse
_____	-1	Almost the same, hardly any worse at all
_____	0	No change
_____	1	Almost the same, hardly any better at all
_____	2	A little better
_____	3	Somewhat better
_____	4	Moderately better
_____	5	A good deal better
_____	6	A great deal better
_____	7	A very great deal better

Continued on next page

4. Since your last clinic visit, has there been any change in your overall emotions related to your overactive bladder problems?

Place "X" next to the statement that most accurately reflects your opinion:

_____ -7 A very great deal worse

_____ -6 A great deal worse

_____ -5 A good deal worse

_____ -4 Moderately worse

_____ -3 Somewhat worse

_____ -2 A little worse

_____ -1 Almost the same, hardly any worse at all

_____ 0 No change

_____ 1 Almost the same, hardly any better at all

_____ 2 A little better

_____ 3 Somewhat better

_____ 4 Moderately better

_____ 5 A good deal better

_____ 6 A great deal better

_____ 7 A very great deal better

Thank you. This completes the questionnaire.

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

SC110198; SCIRP-CTA-R

W81XWH-12-1-0549

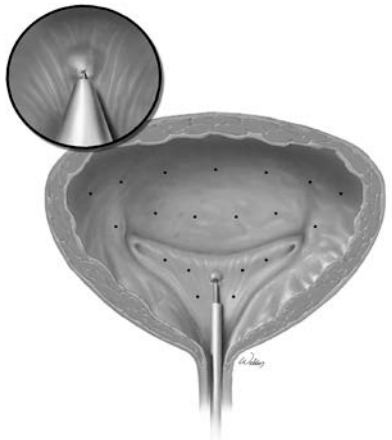
PI: Christopher P. Smith, MD **Org:** Baylor College of Medicine **Award Amount:** 904,516.00

Study/Product Aim(s)

- Screen, enroll, and treat 36 patients randomized to two treatment groups
- Evaluation of biomarkers pretreatment and during follow up

Approach

FDA IND, BCM IRB, and MEDVAMC approvals were granted. HPRO approval with funding notice was received March 2013. The study was closed at MEDVAMC on July 25, 2016 due to lack of accrual. BCM IRB has approved the TIRR Memorial Hermann site and subject accrual is ongoing.



BOTOX Injection Pattern Diagram

Accomplishment: A total of 13 patients have been consented at TIRR. Five subjects have completed the study. Four were screen failures. One was incarcerated and two were withdrawn: one due to non-compliance and the other had other health issues.

Timeline and Cost

Activities FY	12	13	14	15	16	17/18
Regulatory Approvals						
Screening, Enrollment, Treatment						
Biomarker Evaluation						
Follow-up Visits						
Data Analysis/Reporting						
Estimated Budget ($K)	81	356	360	349	390	NCE

Updated: November 2018

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.

CY16-17 Goals – Subject visits and biomarker evaluations

☑ Subject enrollment, follow-up visits, and biomarker evaluation ongoing

CY18 Goal – Study Completion

☑ Subject follow-up visits , biomarker evaluation, and Data analysis/reporting completed

Comments/Challenges/Issues/Concerns

Study closure due to poor enrollment.

Budget Expenditure to Date

Projected Expenditure: $465,000.00

Actual Expenditure: $459.546.32