Department of Veterans Affairs

VA RESEARCH CONSENT FORM

Subject Name: _____ **Date:** _____

Subject Initials: _____

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

H-27457 - A DOUBLE-BLIND, RANDOMIZED STUDY OF THE EFFICACY OF ONABOTULINUMTOXINA (ONABONT-A) VERSUS ORAL TAMSULOSIN IN MEN WITH BPH AND LUTS (PROTOCOL # 02-10-10-05)

BOTOX versus Flomax for BPH and LUTS

Background

Benign prostatic hyperplasia (BPH) is a common condition that affects nearly half of men over age 50 and 90% of men over 80. Lower urinary tract symptoms (LUTS) caused by BPH which may include excessive urinating at night, urinating often, having to hurry to urinate, not being able to start the urine stream, staring and stopping of the urine stream, and not fully emptying your bladder. These symptoms can be very bothersome, can significantly affect your lifestyle, and are costly.

Our site was one of 7 centers involved in a 12-week Phase II study of 100 and 300 units of onaBoNT-A (BOTOX) for the management of BPH. A total of 134 men were enrolled and treated and 125 completed the study. A positive effect of onaBoNT-A was characterized as a 30% or better change in their symptoms.

This study is a clinical research study that is conducted under the FDA (Food and Drug Administration). The onaBoNT-A has been approved for use in humans for other problems but not for prostate problems.

Tamsulosin (Flomax) has been approved by the FDA for the treatment of your symptoms.

You are being asked to participate in this clinical research study because you have BPH and or LUTS.

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.

Purpose

The main purpose of the study is to compare the effectiveness of 200 U onaBoNT-A injected into the prostate versus tamsulosin for the treatment of lower urinary tract symptoms caused by BPH. Changes in the prostate tissue that is removed during the prostate biopsies will also be compared.

Procedures

The research will be conducted at the following location(s):
Baylor College of Medicine, Michael E. DeBakey Veterans Affairs Medical Center, and UT: Health Science Center - Houston.

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The study medications for this study are onaBoNT-A injection, placebo injection, oral (by mouth) tamsulosin (Flomax) and placebo oral drug. For this study, the placebo injection is saline (salt water) and the oral drug is a look-alike capsule that contains no medicine. You will be in ARM 1 (onaBoNT-A injection and placebo capsule that is taken every day by mouth) or ARM 2 (placebo (salt water) injection and a tamsulosin 0.4 mg capsule taken every day by mouth).

You will have 5 clinic visits and 2 telephone visits during this study. Your participation in the study will be about 4 to 5 months.

VISIT 1: Screening:

These procedures and events will be done to see if you are allowed to take part in the study. They will be done after you have reviewed this form and the study doctor or a member of the study has answered all of your questions and you have signed this informed consent form. Your information that is collected for the study are the your initials, date of birth, gender, and Race/Ethnicity. The MEDVAMC requires that your Social Security Number is added to this consent form. This information will not be given to anyone outside of the MEDVAMC system unless required to do so by law. You will be given a unique study identifying number. This number will be entered on all study documents and used throughout the study. All prostate specimens collected as part of the research procedures for this study will be coded so that the results of the tests can not be directly linked to you.

1. You will have a physical examination including a digital rectal examination (DRE). The doctor will insert his gloved finger into your rectum to feel the prostate in order to estimate the prostate's size, shape, and consistency.

2. Your vital signs (pulse, breathing rate, temperature, and blood pressure) will be taken and recorded.

3. You will be asked questions about your medical history and about any medications you are now taking.

4. You will complete the following 5 questionnaires:

- The AUA (American Urological Association) symptom score - asks questions about your urinating symptoms
- BPH Impact Scale - asks questions about how your urinary problems effect your daily life.
- Bladder Function - asks more detailed questions about your urinary habits
- Erectile Function - asks questions in order to determine how your urinary symptoms are effecting your erections

- Ejaculatory Function - asks questions about your ejaculations when having sexual activity

Your responses to these questionnaires will give the study doctor a better understanding of your urinary symptoms and how they are effecting your life.

5. Your urine flow will be tested while standing and urinating into a large plastic funnel that has a sensor in the bottom which measures the force of the urine stream. The amount of urine left in the bladder will be measured using a bladder scanner. The scanner is placed directly on top of the skin over your bladder, which has a gel applied to the surface.

6. You will have about 2 teaspoons of blood draw to test your PSA (prostate-specific antigen) and your complete blood count (CBC). The PSA is a test that screens for cancer of the prostate. The CBC tests to see if you have any illness or infection.

7. You will provide a urine sample that will be tested to see if you have a urinary tract infection or any other problems.

8. You will be given doses of an antibiotic medicine with instructions to take them 1 day before the biopsy, on the day of the biopsy, and on the day after the biopsy.

9. You will be instructed to stop taking your alpha blocker medications 7 days prior to the biopsy.

10. You will be scheduled for Visit 2.

VISIT 2: Biopsy

1. You will be asked about your current medications and if your health has changed or if you have had any problems since your last visit. You vitals signs will be taken and you will provide a urine sample for testing.

2. You will be asked if you took the dose of antibiotic the day before the biopsy and on the day of the biopsy. You will be reminded to take another dose the day after the biopsy.

3. You will receive a Fleet enema. Fleet Enema is a saline (salt water) laxative. Saline laxatives work by drawing water into the colon which helps produce a bowel movement. This provides a soft stool mass and increased bowel action. A bowel movement should be stimulated in 1 to 5 minutes, without pain or spasm.

4. You will undergo a Transrectal Ultrasound (TRUS): In this test, a small probe is placed in the rectum near the prostate in a position similar to the digital rectal examination performed by the doctor. The probe uses ultrasound waves, which are not harmful, to produce an image of the prostate. The procedure usually last approximately 20 minutes from start to finish.

5. A biopsy will be conducted by inserting a tiny needle alongside the TRUS probe to remove a small sample of prostate tissue.

6. You will be given doses of an antibiotic medicine with instructions to take them 1 day before the injection, on the day of the injection, and on the day after the interjection.

7. You will be scheduled for Visit 3.

VISIT 3: Four weeks (plus or minus 3 days) after VISIT 2.

This is the randomization and injection visit.

1. You will be asked about your current medications and if your health has changed or if you have had any problems since your last visit.

2. You will have a physical examination including a DRE and your vital signs will be taken.

3. You will provide a urine sample that will be tested to see if you have a urinary tract infection or any other problems.

4. You will be asked if you took the dose of antibiotic the day before the biopsy and on the day of the biopsy. You will be reminded to take another dose the day after the biopsy.

5. You will have an enema just like you did during Visit 2.

6. You will have a TRUS just as you did in Visit 2.

7. You will be given a local anesthetic to block the pain from the prostate injection.

8. You will be randomized to either :

- ARM 1: onaBoNT-A injection and placebo capsule that is taken every day by mouth

OR

- ARM 2: placebo (salt water) injection and a tamsulosin 0.4 mg capsule taken every day by mouth.

Randomization is the assigning of which treatment group you will be in. It is done by chance, similar to tossing a coin. This is a double blind study which means you nor the study doctor will know which study drugs you are receiving. In case of emergency, the VA pharmacist will be able to tell the doctor which drugs you were given.

9. The study doctor will perform the prostate injection procedure.

10. You will remain in the clinic until you are able to urinate.

11. You will be given the oral study drug to take home with you. The study coordinator will provide you with detailed instructions and a capsule diary so you can record the day and time that you take your study medication.

12. You will be required to use condoms when you engage in sexual activities for 48 hours after the injection procedure.

VISIT 4: Day 3 after the injection procedure

You will be contacted by telephone 3 days after injection to ask you if you are experiencing any symptoms of infection or if bleeding has occurred.

VISIT 5: 1 Week (plus or minus 3 days) after the injection procedure

You will be contacted by telephone about 1 week after injection to ask about any medical problems you may have, what current medications you are taking, and how you are feeling.

VISIT 6: 4 Weeks (plus or minus 3 days) after the injection procedure

1. You will be asked about your current medications and if your health has changed or if you have had

any problems since your last visit.

2. Your vital signs will be taken.

3. You will provide a urine sample for testing.

4. You will complete the following 5 questionnaires as you did at VISIT 1.

5. Your urine flow will be tested while standing and urinating into a large plastic funnel that has a sensor in the bottom which measures the force of the urine stream. The amount of urine left in the bladder will be measured using a bladder scanner. The scanner is placed directly on top of the skin over your bladder, which has a gel applied to the surface.

6. You will return the study drug bottle and your drug diary will be reviewed and discussed with you.

7. You will be given new supply of study drug.

8. You will be scheduled for your next study visit.

9. You will be given doses of an antibiotic medicine with instructions to take them 1 day before the biopsy, on the day of the biopsy, and on the day after the biopsy.

VISIT 7 - END of STUDY: 3 Months (plus or minus 3 days) after the injection procedure

1..You will have a physical examination including a digital rectal examination (DRE)

2. Your vital signs will be taken.

3. You will be asked about your current medications and if your health has changed or if you have had any problems since your last visit.

4. You will return you study drug product packaging and your study drug diary will be reviewed and discussed with you.

5. Your urine flow will be tested while standing and urinating into a large plastic funnel that has a sensor in the bottom which measures the force of the urine stream. The amount of urine left in the bladder will be measured using a bladder scanner. The scanner is placed directly on top of the skin over your

bladder, which has a gel applied to the surface.

6. You will complete the following 5 questionnaires as you did at visits 1 and 6.

7. You will have about 1 teaspoon of blood draw to test your PSA (prostate-specific antigen)

8. You will provide a urine sample that will be tested to see if you have a urinary tract infection or any other problems.

9. You will undergo a Transrectal Ultrasound (TRUS): In this test, a small probe is placed in the rectum near the prostate in a position similar to the digital rectal examination performed by the doctor. The probe uses ultrasound waves, which are not harmful, to produce an image of the prostate. The procedure usually last approximately 20 minutes from start to finish.

10. A biopsy will be conducted by inserting a tiny needle alongside the TRUS probe to remove a small sample of prostate tissue.

This will end your participation in this research study.

Specimens/Tissues:

The blood and urine specimens collected during the screening visit are routine for patients with your symptoms and will be handled according to standard of practice. The test results will be included in your research and medical charts.

You will have about 3 teaspoons of blood drawn during your participation in this study.

Your prostate tissue that is collected during this study will be coded before being sent to Dr. Gustavo Ayala's laboratory located at the University of Texas Medical School - Houston for testing to see about the changes caused by the BOTOX injection. The tissue is coded with your Subject ID number so that the laboratory personnel will not know it belongs to you. The study doctor will have the only log that links your name to your Subject ID number.

If any of your tissues remain at the end of the study, they will be destroyed. The tissues will not be released to anyone not listed as an investigator on the protocol, nor will they be sold or transferred to any third party. You will not be able to get the tissues back. Upon your written request to Dr. Smith (Baylor College of Medicine, Scott Department of Urology, 1709 Dryden, Suite 1600, Mail Stop

BCM380, Houston, TX 77030), the tissues will be destroyed but the data collected up until that time will not be deleted.

The study's data will be analyzed by the study's doctors who are affiliated with the VA and Baylor College of Medicine. Information provided to the doctors will be coded so they will not be able to link your name with the data.

Confidentiality

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Full Social Security #
- Partial Social Security # (Last four digits)

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law.

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts

BOTOX® (onaBoNT-A): It is expected that some participants may have some or all of the following side effects when given BOTOX®. 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 BOTOX®. These reactions include allergic reaction, skin rash, itching, swelling, and difficulty in breathing.

It is a rare possibility that the injection of BOTOX® 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). It is not known if BOTOX® actually caused these problems.

It should not be used when infection is present at the injection site or in people known to be sensitive to BOTOX®.

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 BOTOX®.

There are also possible risks of not being able to empty the bladder, diarrhea, and infection as a result of the BOTOX® injection.

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.

Recently, bladder stones have been reported in monkeys receiving multiple BOTOX ® injections into the prostate. The significance of this finding is not currently known.

It is important that you to inform your study staff about your other medical conditions. In particular any nerve-muscle disorders because patients with certain diseases may be at increased risk of clinically significant or even fatal effects.

TAMSULOSIN (Flomax): Tamsulosin capsules may cause a sudden drop in blood pressure upon standing, especially after the first dose or when changing doses. Symptoms may include fainting, dizziness, and lightheadedness.

Allergic reactions may include rash, itching, and hives. Rare and more serious allergic reactions may also include swelling of face, tongue, or throat, and difficulty breathing.

Priapism (a painful erection that will not go away) may occur.

During cataract surgery, a condition called intra-operative floppy iris syndrome (IFIS) can happen if tamsulosin is being taken or has been taken in the past.

Common side effects of tamsulosin capsules may include runny nose, dizziness, and decreased semen.

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 EFFECT: Some people in the study will get placebo injection instead of BOTOX® solution. Taking placebo is the same as not receiving anything for your BPH symptoms. If you take placebo during the study, it is possible that your BPH symptoms may get worse.

Some people in the study will get placebo capsule instead of Tamsulosin capsule. Taking placebo is the same as not receiving anything for your BPH symptoms. If you take placebo during the study, it is possible that your BPH symptoms may get worse.

Please ask the study doctor or study staff if you have any questions about placebo.

ANTIBIOTIC: 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, vaginal infection. It may also cause confusion, dizziness, feeling shaky, unusual hunger, headaches, irritability, pounding heart or very fast pulse, pale skin, sweating, trembling, weakness, unusual anxiety, and coma. Coma is a state of unconsciousness in which a person cannot be awakened; fails to respond normally to painful stimuli, light, or sound; lacks a normal wake-sleep cycle; and does not initiate voluntary actions

You should tell a member of the study team if you are taking a diabetes medicine when your study doctor is considering prescribing an antibiotic, and also if you have low blood sugar or symptoms of it while taking a the antibiotic. For patients with diabetes, your study doctor may ask you to check your blood sugar more often while taking the antibiotic.

TRANSRECTAL ULTRASOUND (TRUS): The ultrasound rarely results in physical discomfort but you may experience some anxiety before and during the procedure.

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.

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

LOSS OF CONFIDENTIALITY: The loss of confidentiality regarding research information is a possibility; although, the risk is very small. Your prostate tissue specimens will labeled with your subject code before being sent to Dr. Ayala's laboratory. The laboratory personnel will not be able to know that these specimens are yours. Study documents may include your initials and subject code but no other identifying information.

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Subject Initials: _____

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

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BIRTH CONTROL: Because of the possibility of diffusion of BOTOX® into seminal fluid, and no evidence to the contrary, you MUST use condoms if you engaged in sexual intercourse during the 48 hours after the injection.

There may be unknown risks or discomforts involved. Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

The benefits of participating in this study may be: to see an improvement of your symptons from the BOTOX® injection within one week after injection. Your participation may help to determine new treatments for BPH and LUTS. 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: watchful waiting, medical therapy with approved drugs, or surgical treatment.

Investigator Withdrawal of Subject from a Study

The investigator or sponsor may decide to stop you from taking part in this study at any time. You could be removed from the study for reasons related only to you (for example, if you move to another city, if you do not take your study medication, or if you have a serious reaction to your study medication) or because the entire study is stopped. The sponsor, investigator, Food and Drug Administration, or Institutional Review Board may stop the study at any time.

Subject Costs and Payments

The study investigative products (injections and oral medications) and anesthesia will be provided at no cost to you.

All other events and procedures are considered standard of care. Your participation will not affect the way you now pay for medical care at the VAMC.

You will not be paid for taking part in this study.

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.

Research Related Injury

If you experience any injury related to your participation in this research study, please contact Dr. Christopher P. Smith at 713-798-4001 immediately. He will provide instructions on how to proceed.

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Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, CHRISTOPHER PATRICK SMITH, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: CHRISTOPHER PATRICK SMITH at 713-798-4001 24 hours a day.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office 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.

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A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

_____	_____
Subject	Date
_____	_____
Investigator or Designee Obtaining Consent	Date
_____	_____
Witness	Date