Biomedical Research Alliance of New York LLC
Institution Name (use the parent institution, not the particular hospital)

Subject Information and Informed Consent Form

Protocol Title A Phase 1Multicenter Study Evaluating the Safety and Potential Activity Of Two Escalating Doses of *h*Maxi-K Gene Transfer By Direct Injection into the Bladder Wall In Female Participants With Idiopathic (Non-Neurogenic) Overactive Bladder Syndrome and Detrusor Overactivity: Double Blind, Imbalanced Placebo Controlled Design Within 2 Sequential Active Treatment Groups

Protocol Number ION 03-OAB

Sponsor Ion Channel Innovations, LLC
969 Park Ave., 1G
New York, NY 10028

Principal Investigator **Principal Investigator Name**

Institution Address **Principal Investigator Address**

Telephone **Principal Investigator Telephone number**
24 Hour Telephone **Principal Investigator 24 hour Emergency Telephone number**

PURPOSE OF THE SUBJECT INFORMATION AND CONSENT FORM
INTRODUCTION:
The purpose of this document is to inform you in writing of the purposes of this research, a description of the procedures to be followed, possible risks and discomforts, precautions and the basic ground rules which will govern this research study. Please, read this informed consent form and ask as many questions as you like.

The staff and your study doctor are available to talk about them. When you have completed reading, and if you decide to join in the study, you will be asked to initial and date each page and sign the last page. Your signature means that you have read and have also listened to a spoken explanation of the information to follow.

Please read this form carefully before you make your decision. You may refuse to participate in this study and this decision will not be held against you, nor will it change any matters between you and this office, and you will continue to receive the same medical care.

FINANCIAL DISCLOSURE
Ion Channel Innovations, LLC is providing funds to **Principal Investigator name** on a per subject basis for conducting this research study.

PURPOSE: NATURE AND PURPOSE OF THE STUDY
You are being asked to be a part of this research study because you have a condition called overactive bladder.

The purpose of this study is to evaluate the safety of a new product that uses human gene transfer called *h*Maxi- K when it is given to patients with overactive bladder. Human Gene transfer is a new type of therapy that is the process of placing genetic material (DNA or RNA) into a person. At present, human gene transfer is experimental and is being studied to see whether it could treat certain health problems by making proteins that treat the problem. Human gene transfer may help improve genetic disorders, (such as, sickle cell anemia, hemophilia, and cystic fibrosis). This type of experimentation is sometimes called “gene therapy” research.

*h*Maxi-K is a “naked,” human cDNA. Compared to other gene therapies, hMaxi-K does not use viruses to make them effective. *h*Maxi-K does not correct a genetic defect. Instead, *h*Maxi-K cDNA produces a protein that is expected to cause smooth muscle cells to relax. *h*Maxi-K is injected directly into the bladder wall where the gene is available and taken up by the smooth muscle cells of the bladder. Two different dose levels of *h*Maxi-K will be studied, (16,000 and 24,000 microgram doses). You will receive 20 to 30 injections directly into your bladder wall of only one of these doses or Placebo (a solution containing no active drug- sugar and salt water solution). All of the women in the study will either be those who no longer have periods or cannot have children and have symptoms of overactive bladder that include:

- Frequent urination (that is, having to go to the bathroom more than 8 times per day);
- Symptoms of urinary urgency where you experience a sudden need to pass urine, which is difficult to hold back or the complaint of waking at night two or more times to urinate; and/or
- Urge urinary incontinence which is the complaint of leakage of urine that cannot be stopped accompanied by or immediately preceded by urgency on the average of 5 times per week.

This gene transfer product that you may receive is not approved by the Regulatory Authorities (the governmental agencies responsible for approving new drugs such as the Food and Drug Administration [FDA]) for use in treating your condition and is therefore considered to be experimental or "investigational."

Currently, there are several approved medications to treat overactive bladder including drugs (pills) such as: Detrol® (oxybutynin), Enablex® (darifenacin), VESIcare® (solifenacin), Ditropan® (tolterodine), Myrbetriq® (mirebegron) and Botox® (Botulinium Toxin A) by injection into the bladder wall. You are not permitted to use these drugs while you are in this study.

NUMBER OF SUBJECTS AND DURATION OF STUDY

Approximately 18 women will participate in this study. Each woman's participation in the study will last for up to 184 days (up to 7 months). You will have a total of 9 visits to the office and a telephone contact 1 day post dosing and 3 days post dosing to evaluate for any new complaints. If you are randomly assigned to receive hMaxi-K, you will be followed for an additional 18 months after the last study visit has completed. The office will contact you at 6 month intervals by phone to evaluate for any safety concerns.

During the study you will have to complete certain study-specific tests. Details about the study-specific tests, examinations, and questionnaires are included in this form.

DESCRIPTION OF THE RESEARCH STUDY

Study Medication:

Two different dose groups of *h*Maxi-K will be tested in this study: 16000 micrograms and 24000 micrograms. You could receive one of these 2 doses or also receive placebo (no active drug – sugar and salt water solution).

A total of up to 9 women will be enrolled in each dose group. For the 9 women per dose group, 6 will be randomly assigned *h*Maxi-K and 3 subjects randomly assigned placebo. The first 9 women will be assigned 16000 micrograms or placebo; the second 9 subjects will be assigned 24000 micrograms or placebo. That is, depending on which dose group you are in, you will be randomly assigned (like flipping a coin) to one of the 2 treatment groups (*h*Maxi-K or placebo). Your chance of getting *h*Maxi-K is approximately 2:1 or nearly two out of three.

Study Procedures:

Visit 1 (2 weeks prior to injection): If you agree to take part in this study, your study doctor will check whether or not you belong to the group of women that is eligible for the study. You will then undergo study specific tests, including a medical history, physical examination, a fasting blood sample test, urine tests, an electrocardiogram (ECG), and bladder scan to measure urine volume after you urinate using a wand that reflects sound waves over your abdomen). You will also be required to complete some questionnaires and diaries describing your condition and state of health. You will also be catheterized (a very small tube will be passed into your bladder) to collect a urine specimen to make sure you do not have any urinary tract infection.

Before you leave the clinic you will be scheduled for your second Screening visit which will occur within 6 days after visit 1. However, in some cases if scheduling permits you may have the procedures required at visit 1A performed at Visit 1(cystometry and urine cultures before and after cystometry). A cystometry is a procedure to test your bladder function and requires that a catheter (small narrow tube) be put into your bladder through your urethra (a canal that goes from your bladder to the outside of your body enabling you to urinate) and a small catheter will be

placed into the rectum. Only if Visit 1A is scheduled on a separate day, you will be given a diary that you will need to complete for approximately 6 days or less prior to visit 1A to see if you are completing the diaries correctly; a member of the study staff will be calling you to remind you to complete your diary. You will also be given a cylinder for urine measurement at home and instructed about using your pads. You will need to bring in a plastic bag, with all the pads you have worn for the 3 days prior to Visit 1A and a clean pad to use as a baseline. You will be instructed to not take any antiplatelet or non-steroidal anti-inflammatory drugs (such as aspirin, ibuprofen, naproxen, etc) and anticoagulant drugs (such as warfarin, Coumadin, heparin, etc) that may increase bleeding for at least 10 days prior Visit 2. All visit 1 study-specific tests will only be performed after you sign this informed consent form.

Visit 1A (14-8 days prior to injection):
Your study doctor will evaluate your visit 1 information and procedures to confirm your eligibility. Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit. Upon doing so, you will have a cystometry. As above, cystometry is a procedure to test your bladder function and requires that a catheter (small narrow tube) be put into your bladder through your urethra (a canal that goes from your bladder to the outside of your body enabling you to urinate) and a small catheter will be placed into the rectum. The cystometry will provide information that will help your doctor determine how your bladder function (how bad your overactive bladder condition is). In total, this procedure will last about 60 minutes.

Before you leave the clinic you will be scheduled for your next visit which will occur 8 days after this visit.

You will have some urine collected for culture and testing prior to the cystometry and following the procedure.

You will be given a diary that you will need to complete for 7 days prior to the next visit (visit 2); a member of the study staff will be calling you to remind you to complete your diary. You will also be given a cylinder for urine measurement at home and instructed about using your pads. You will need to bring in a plastic bag, with all the pads you have worn for the 3 days prior to Visit 2 and a clean pad to use as a baseline.

You will be instructed to not take any non-steroidal anti-inflammatory drugs (such as aspirin or ibuprofen, naproxen, etc) that may increase bleeding for at least 10 days prior Visit 2.
The results of all the procedures and questionnaires done at Screening Visit 1 and 1A, your completed patient 7 day diaries, and 3 days of used pads will be used at Visit 2 by your study doctor in the evaluation of your study participation.

Visit 2: (Baseline visit/Study injection)
Your study doctor will evaluate your visit 1 and 1A information and procedures to confirm your eligibility. Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit.

If you are eligible and agree to continue to be in the study, you will be asked questions about your health since the last visit, answer questions about how your overactive bladder condition affects your quality of life, have a physical examination (including a pelvic exam), urine specimen collected, blood drawn, blood pressure taken and an ECG (recording of the electrical activity of the heart using sensors placed on your chest) before giving you the study drug.

Administration of Study Drug. The drug will be given by 20 to 30 direct injections into the wall of your bladder after placement of a cystoscope (a very small telescope type instrument allowing the doctor to see the inside of your bladder). You will have a local anesthetic administered prior to the drug administration so hopefully the procedure should be relatively pain free.

After the drug is given to you, your blood pressure will be recorded every 15 minutes for the first 2 hours. You will be required to stay at the study site for at least 2 to 3 hours after dosing. You may be asked stay longer if your doctor believes it is necessary.

At 2 hours after dosing you will have blood drawn again to test for study drug levels. At discharge from the clinic you will also be asked to leave a urine specimen for testing to make sure you have no infections after the procedure and to test for study drug levels. You will be given an antibiotic to take on the day of visit 2 and for 2 days thereafter.

You will be given a diary that you will need to complete for 7 days prior to visit 3; a member of the study staff will be calling you to remind you to complete your diary. You will also be given a cylinder for urine measurement. You will need to bring in a plastic bag with any pads you have worn for the 3 days (and a clean pad to use as a baseline) prior to Visit 3, which will be 7 days after study injection.

1 and 3 Day Telephone Contact
On day 1 and 3 post injection, after you have received the study drug, someone from the office will give you a call at home to evaluate for assessment of adverse reactions and to see how you are doing. However if you have any problems or complaints at any time during the study you should call the office immediately. If you do have complaints, you may be asked to come for an unscheduled visit for further evaluation.

Visit 3: (8 days post injection)
During visit 3 you will have the following examinations: complete physical exam including vital signs (blood pressure, heart rate, and temperature), ECG, various fasting blood samples for routine analysis, and urine and blood samples to test if drug is still detectable in your urine or blood. Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit. You will be asked to complete various questionnaires to study any changes in how your overactive bladder condition affects your life. You will be given a diary that you will need to complete for 7 days prior to visit 4; a member of the study staff will be calling you to remind you to complete your diary. You will also be given a cylinder for urine measurement. You will need to bring in a plastic bag with pads you have worn for the 3 days and a clean pad to use as a baseline (and a clean pad to use as a baseline) prior to the next visit.

Visits 4: (15 days post injection)
Two weeks after you were given the study drug you will return to the office with your completed patient diaries and all used pads worn for 3 days prior to this visit (and a clean pad to use as a baseline). Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit. At this visit you will have a physical examination and a bladder scan will be done, as well as collection of a fasting blood and urine samples. You will also have a physical examination, measurement of vital signs, and complete questionnaires. You will be given a diary that you will need to complete for 7 days prior to visit 5; a member of the study staff will be calling you to remind you to complete your diary. You will

also receive a cylinder for urine measurement. You will need to bring in a plastic bag with any pads you have worn for the 3 days prior to the next visit (and a clean pad to use as a baseline).

Visit 5: (8 weeks post injection)
One month after you were given the study drug you will return to the office with your completed patient diaries and all used pads worn for 3 days prior to this visit (and a clean pad to use as a baseline). Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit. At this visit you will have a repeat cystometry (as described above in Visit 1) performed to study your bladder muscle activity as well as a physical examination, vital signs, fasting blood and urine samples, and the completion of questionnaires. At discharge you will pass some urine for testing to make sure you have no infections after the catheter was removed.

You will be given a diary that you will need to complete for 7 days prior to visit 6; a member of the study staff will be calling you to remind you to complete your diary. You will also be given a cylinder for urine measurement. You will need to bring in a plastic bag with any pads you have worn for the 3 days prior to the next visit (and a clean pad to use as a baseline).

Visit 6 (8 weeks post injection):
Two months after you were given the study drug you will return to the office with your completed patient diaries and all used pads worn for 3 days prior to this visit (and a clean pad to use as a baseline). Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit. At this visit you will have your vital signs taken, bladder ultrasound conducted, urine and fasting blood samples collected to test if drug is still detectable in your urine or blood, and questionnaires will also be done. At discharge you will be given a diary that you will need to complete for 7 days prior to visit 7; a member of the study staff will be calling you to remind you to complete your diary. You will also be given a cylinder for urine measurement. You will need to bring in a plastic bag with any pads you have worn for the 3 days prior to the next visit (and a clean pad to use as a baseline).

Visit 7: (12 weeks post injection)
Three months after you were given the study drug you will return to the office with your completed patient diaries and all used pads worn for 3 days prior to this visit (and a clean pad to use as a baseline). Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit. At this visit you will have a physical examination, vital signs taken, fasting blood and urine samples will be obtained and questionnaires will also be done.

Visit 8: (24 weeks post injection)
Six months after you were given the study drug you will return to the office with your completed patient diaries and all used pads worn for 3 days prior to this visit (and a clean pad to use as a baseline). Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit. At this visit you will have a physical examination, ECG, a repeat cystometry (as described above in Visit 1A), a bladder scan to check for residual urine, your vital signs taken, fasting blood and urine samples collected, and questionnaires will also be done.

Following Visit 8, the study personnel will contact you for an additional 18 months (approximately every 6 months), to review any problems or complaints you may be have.
Blood and urine samples will be collected at various time points. Fasting blood will be collected up to 9 times during the study as described above for the different study visits. The total amount

of blood to be drawn throughout the study (over 6 months) is approximately 115 ml that is equal to about 9 tablespoons. The samples will be sent to a laboratory contracted by your study doctor for analysis. The site staff may contact you before each scheduled visit to remind you to fast. You will be asked to not exercise or do strenuous activities prior to any blood sampling. Urine samples will also be collected up to 11 times during the study as described above. These urine samples, besides standard tests, will test for signs of urinary tract infection. Eight urine and 8 blood samples will also be taken to test for the presence of gene transfer product (study drug) throughout the visits. At Visit 2, you will have blood and urine samples taken twice to measure for the study drug - before dosing (at the same time as other blood and urine safety tests are taken) and again at 2 hours after dosing. At Visits 3 to 8, blood and urine samples to test for study drug will be taken only once when blood and urine are collected for other safety tests. During the 18 month follow-up, if there is any hMaxi-K gene still measured in your blood or urine at Visit 8, then at least 2 additional consecutive monthly samples of blood and/or urine will be taken until there is no more evidence of the gene.

At each visit you will be asked about your medications and any changes to your health since receiving the study injection. You must tell the clinic personnel of any changes to or additions to your regular medications.

There may be reasons why you cannot participate in this study. The study doctor or study staff will discuss these reasons with you.

RISKS AND DISCOMFORTS
You must understand that there may be risks to you while you a part of this study. Your medical condition may not improve or may worsen while you are part of the study. As with any investigational drug, it is possible that you may experience some discomfort or adverse reactions (side effects) associated with the use of the drug that are not known prior to this study.

Possible Risks with *h*Maxi-K:
A study looking at the safety and effects of *h*Maxi-K in 20 men with impotence has been completed. Although *h*Maxi-K was given in a different organ in this study (injected into a blood vessel in the penis), few adverse events were seen and few were thought to be due to the gene transfer product (see the next section). In addition a study evaluating the active drug in 16 women with overactive bladder such as you have has been completed. As with any investigational drug, there remains potential risk for adverse effects after a gene product is given that changes the flow of water and salts (which is how *h*Maxi-K works). Any organ whose function could be affected by a change in the flow of water and salts could have bad effects after the injection of *h*Maxi-K, such as blood vessels and the brain. There could be local effects in the bladder from the catheter or the solution such as infection, local pain, or irritation. There could possibly be some bleeding from the injections and blood in the urine after the procedure. An objective group of doctors called the Data Safety Monitoring Board will also be reviewing all the data that comes from this study to ensure that any problems are addressed quickly and to advise the clinic if it is necessary to stop the administration of the drug.

Administration of *h*Maxi-K in humans has shown that the drug is well tolerated with few side effects reported. To date, as above, a total of 20 men have been given *h*Maxi-K in a trial for impotence; three men have received 500 micrograms, three received 1000 micrograms, three men received 5000 micrograms, two men have received 7500 micrograms, three men received 8000, three men received 12000 micrograms, and three men received 16000 micrograms (the lowest dose in the study you are taking part in). In these men only one of the events was considered related to the study drug, *h*Maxi-K, and was reported by one of the men who received

12000 micrograms as a tingling warmth in the penis.

Other adverse events that were reported but **considered unrelated** to the study drug, *h*Maxi-K included the following:

Heart arrhythmia (abnormal heart rhythm),, Kidney stones , Acid reflux, Sciatic pain (pain that runs down the back of leg), Upper respiratory infection, Parasitic intestinal infection, Foot swelling, Flu like symptoms, Hand pain, Platelet changes, Common cold, Brief penile pain.
In the female participants for the overactive bladder study ten participants received the 5000 microgram dose (7 in this group completed the study; 3 discontinued early seeking other treatment for their overactive bladder symptoms), 6 participants received the 10000 microgram dose and 5 participants received placebo (all participants completed in the 10000 microgram and placebo groups). There were no serious adverse events reported or a withdrawal for an adverse event.

In the 5000 microgram dose, **possibly related** adverse events were reported in one subject each, and included urinary tract infection, a heart block (abnormal heart rhythm, fatigue, headache, shaking chills, and insomnia.

Unrelated events were reported and included headache; rash; fractured left (big) toe; infection left (big) toe; worsening of fat tissue near the vagina; knee tendonitis; right kidney cyst benign; worsening of depression; worsening of acid reflux/indigestion; elevated blood creatinine (lab test for kidney function); diffuse loss of renal parenchyma (kidney tissue); hypertensive renal disease; atypical chest pain; CK and CK-MB elevated (lab tests possibly secondary to high blood pressure caused by kidney disease) diarrhea; vomiting, hiatal hernia; bacteriuria (bacteria in the urine); constipation; fatigue; fall; upper lip skin scrape secondary to fall; acne on face; and urinary tract infection.

In the 10000 microgram dose group, adverse events were all considered **unrelated** and included in one subject each common cold; elevated blood pressure; worsening of urge incontinence; tension headache; low back pain; fall; pain on urination (dysuria); elevated liver function tests; and hepatitis C.

In the **placebo** group, heart palpitations were reported in one participant, which were considered **possibly related**, mild severity, and occurred 6 days post treatment. **Unrelated events** for placebo that were reported in one participant each included slight irritation at the vulva, fractured pelvis (left side) and wrist fracture (left); 4 unrelated urinary tract infections (UTIs) were reported in 2 participants.

No clinically significant changes were seen in the physical examinations or laboratory values during the study (except for those changes in laboratory tests mentioned above in one participant who received 5000 micrograms and in one participant who received 10000 micrograms which were considered unrelated to study gene transfer). *h*Maxi-K is a unique therapy and therefore there are no similar drugs for comparison of side effects. As with any investigational drug, there is a possibility of unknown side effects.

Also as with any drug, there is a potential for an allergic reaction. Since *h*Maxi-K is a foreign substance to the body, the body may produce antibodies (protein produced by the body to neutralize or destroy foreign substances in the body) against *h*Maxi-K which can possibly lead to allergic reactions. Allergic signs may also occur from other compounds, such as those in the

placebo, in certain individuals. Therefore, please notify your study doctor immediately if you experience itching, rash, nausea, fever or other signs.

Pregnant patients (or a patient who could get pregnant) are excluded from the study. The safety of *h*Maxi-K in pregnant and/or nursing women has not been established. Therefore only women who are postmenopausal or who have had surgical sterilization (hysterectomy, tubal ligation) will be allowed in the study. It is extremely important to tell your study doctor if you are pregnant, are still able to become pregnant, or become pregnant during the course of this study.

Laboratory tests suggest that *h*Maxi-K breaks down or disintegrates if it is in the urine longer than 30 minutes.

However, there is the risk that you could still pass some gene transfer product in your urine. You are asked to not have sexual intercourse for the first 24 hours after *h*Maxi-K is put into your bladder.

Risks of Cystometry
Insertion of a bladder catheter into the bladder has some minimal risks. They include urinary tract infection and irritation. Your urine will be collected to test for any infections and you will be treated with appropriate antibiotics if they occur.

Risks of Cystoscopy:
Insertion of a cystoscope into the bladder has some minimal risks. They include urinary tract infection and irritation. There also may also be some slight blood in the urine after injection of the drug into your bladder wall. Bleeding following injection at a puncture site is not uncommon. Your urine will be collected to test for any infections and you will be treated with appropriate antibiotics if they occur.

Risks of Blood Draws:
Possible side effects from blood drawing include: faintness, inflammation (redness and swelling) of the vein, pain, bruising, bleeding at the site of puncture, and a slight possibility of infection at the site of the needle stick.

Medical supervision will be provided throughout the study. If indicated, you will be treated appropriately for any adverse reaction should such occur. If you experience any side effects or research-related injury, contact:

Principal Investigator name and telephone number

Potential Benefits:
The reason for doing this study is to test the safety of different doses of *h*Maxi-K given by injection in participants with overactive bladder syndrome. Although there is no human experience that gene transfer injections could help improve the function of the bladder for some participants there are animal data that indicate that *h*Maxi-K might have a potentially beneficial effect on people experiencing urgency. You may not benefit from being in this research study. However, the information learned from this study may, benefit other people with this condition in the future. You will not have access to the study drug after the study.

ALTERNATE THERAPY
*h*Maxi-K is a unique therapy and therefore there are no similar drugs for comparison. Common side effects of other drugs used to treat overactive bladder include dry mouth, dry eye, thinking

problems, memory loss and constipation. These other drugs which are given as pills include Detrol® (tolterodine) and Ditropan XL® (oxybutynin), Enablex® (darifenacin), Vesicare® (solifenacin), Sanctura® (tospium) and Myrbetriq® (mirebegron). In addition, Botox® (Botulinium Toxin A) is a drug given by injections into the bladder wall to inhibit bladder contractions. Botox® (Botulinium Toxin A) is associated with urinary retention where you are unable to urinate and therefore need a catheter placed into your bladder for possibly a long duration.

NEW FINDINGS
Any new findings that develop or are reported by the Sponsor during the research that might change your mind about continuing to take part in this study will be provided to you as they become available.

COST
All study medication and study-related procedures will be provided at no cost to you for your participation in this study. There will be no additional costs to you for taking part in this study.

PAYMENT FOR PARTICIPATION
You will be reimbursed for your participation in this study. For details, refer to the payment schedule below:

Study Visit Amount Form of payment (cash/check)

Study Visit	Amount
Visit 1/1A- Screening	$
Visit 2 - Baseline	$
Telephone Follow/up	$
Visit 3 – Week 1	$
Visit 4 – Week 2	$
Visit 5 – Week 4	$
Visit 6 – Week 8	$
Visit 7 – Week 12	$
Visit 8 – Week 24	$
Telephone Follow-up	$
	Additional $ /visit to test for study drug or other unscheduled visit repeat assessments

Should you discontinue the study for any reason you will be paid for the time you have been in the study.

SUBJECT RESPONSIBILITIES
As a subject in this research study, it is expected that you will carefully follow the instructions of the doctor and staff. You are expected to:

- Read this Subject Information and Consent Form and ask as many questions as needed.
- Provide the study doctor with a complete history of illnesses (and medications) you've had in the past.
- Provide the study doctor with the name, address, and phone number of your current regular doctor, and state whether or not the study doctor can contact your regular doctor about your being in this study and request your medical records from him/her.
- Keep to the schedule of visits and, if there is a problem, call the study staff to reschedule.
- Complete all tests, procedures, and questionnaires to the best of your ability.
- Report any symptoms/side effects you may be experiencing to the study doctor.
- Inform the study doctor or study staff of any drugs you may have taken between visits.
- Ask questions during the study about anything that may concern you.
- Do not take medications that the study doctor has asked you not to take while participating in the study.
- Do not donate blood while you are participating in the study and for at least one month after you have completed the study.

COMPENSATION FOR RESEARCH-RELATED INJURY

You may be exposed to risk of injury from participation in this study. If injury occurs, all available treatment choices will be considered and given to you by the investigator. In the event of any physical and/or medical injury resulting from your participation in this research project, the Sponsor (Ion Channel Innovations, LLC) will pay medical expenses for any medical problems caused by the study procedures or study drug provided that the study drug was given as directed by your study doctor and/or study staff, and only if the costs are not covered by your medical or hospital insurance or by third party or governmental programs. No additional payments will be available. You must follow the directions of the study doctor and/or study staff to be eligible for this coverage. There is no provision for payment for medical care or for monetary payment from (**Name of Principal Investigator's institution**) for any study-related injury. No other compensation will be offered by ION Channel Innovations, LLC or institution or the Biomedical Research Alliance of New York.

LEGAL RIGHTS

By signing this form, you have not given up any of the legal rights that you otherwise would have been entitled to as a participant in a research study.

CONFIDENTIALITY

The study doctor and staff will collect information about you during the study that will be entered into a database. Your name will not be in the database, but your data will be assigned a specific subject number.

To the extent allowed by law, every effort will be made to keep your personal information confidential.

However, information from this study will be submitted to the study sponsor and to the U.S. Food and Drug Administration (FDA). It may be submitted to governmental agencies in other countries where the study drug may be considered for approval. Medical records, which identify you and the consent form signed by you, will be looked at by the sponsor or the sponsor's representatives and may be looked at by the FDA and other regulatory agencies, the Institutional Review Board, and the Biomedical Research Alliance of New York.

While these parties are aware of the need to keep your information confidential, total confidentiality cannot be guaranteed. The results of this research project may be presented at

meetings or in publications; however, you will not be identified in these presentations and/ or publications.

A description of this clinical trial will be available on *www.ClinicalTrials.gov*, as required by U.S. Law.

This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

AUTHORIZATION TO USE AND DISCLOSE PERSONAL HEALTH INFORMATION

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify you. If you choose to be in this study, the study doctor will get personal information about you. This may include information that might identify you. The study doctor may also get information about your health, including:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Information obtained during this research about laboratory test results
- Results from diagnostic and medical procedures including but not limited to X-rays, physical examinations and medical history
- Billing records
- Information about your health may be used and given to others by the study doctor and staff. They might see the research information during and after the study.
- Your information may be given to the sponsor of this research. "Sponsor" includes any persons or companies that are working for or with the sponsor (Ion Channel Innovations, LLC), or are owned by the sponsor. Information about you and your health which might identify you may be given to:
- The U.S. Food and Drug Administration
- Department of Health and Human Services agencies
- Governmental agencies in other countries
- Biomedical Research Alliance of New York (BRANY)
- The Institutional Review Board
- Accrediting agencies
- Data Safety Monitoring Boards
- Health Insurers/Payors

Your personal health information may be further shared by the groups above. If shared by them, the information will no longer be covered by the U.S. federal privacy laws. However, these groups are committed to keeping your personal health information confidential. If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others without your permission.

Information about you and your health that might identify you may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done, and they will be reviewing your information for this purpose. The

information may be given to the FDA. It may also be given to governmental agencies in other countries. This is done so the sponsor can receive marketing approval for new products resulting from this research. The information may also be used to meet the reporting requirements of governmental agencies.

This authorization does not have an expiration date. If you do not withdraw this authorization in writing, it will remain in effect indefinitely.

By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. You do not have to sign this consent form. If you choose not to sign this consent form, you will not be able to be in this research study. Your decision not to sign this consent form will not have any effect on your medical care and you will not lose any benefits or legal rights to which you are entitled.

You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you may not be allowed to look at or copy your information until after the research is completed.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor at the address on the front of this informed consent form. If you withdraw your permission, you will not be able to continue being in this study, but you will not have any penalty or loss of access to treatment or other benefits to which you are entitled. When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Notice Concerning HIV-Related Information: The recipients of HIV-related information are prohibited from redisclosing it without your authorization unless permitted to do so under federal or state law. You also have a right to request a list of people who may receive or use your HIV-related information without authorization. If you experience discrimination because of the release or disclosure of HIV-related information, you may contact the New York State Division of Human Rights at 212-480-2493 or the New York City Commission on Human Rights at 212-306-7450. These agencies are responsible for protecting your rights. Because this study involves gene transfer, safety information must be reported to the Recombinant DNA Advisory Committee of the National Institutes of Health (NIH) and Institutional Bio-safety Committee (IBC), a group of scientist and non-scientists who review the study in accordance with NIH guidelines. This information is available to the public. However, no information by which participants can be identified will be reported with the safety information.

VOLUNTARY PARTICIPATION

Your decision whether or not to take part in this research study is completely up to you. There will be no penalty or loss of benefits to you if you decide not to participate. In addition, you may withdraw from this study at any time for any reason. There will be no penalty if you decide to withdraw. Should you decide to stop being a part of this study, you must notify your study doctor that you wish to withdraw. If you decide to withdraw, it will be necessary for you to return to the study center for a final visit. This will assist your study doctor in determining if you have any continuing medical problems. You can also discuss with your study doctor how to best continue your medical care.

WITHDRAWAL
The study doctor, the Sponsor company, and the FDA have the right to stop the study or your participation in it at any time, with or without your consent, for any reason, including the following: if you have a side effect from the study drugs; if you need a treatment not allowed in this study; if you do not keep appointments; if you do not take the study drug as instructed; or if the study is canceled by the FDA or the Sponsor company.

QUESTIONS
You have the right to ask questions concerning the possible risks of this study at any time. You will be told of any safety information related to the study or study drug.
If you have questions about the study or experience any research-related injury, contact:
Principal Investigator or his/her associates: **Principal Investigator name**

Telephone Number(s): M-F: Principal Investigator telephone number (day and after hours)
If you have questions about your rights as a research subject, you may contact the IRB at: (516) 470-6900.

SUBJECT'S STATEMENT OF CONSENT
I voluntarily agree to participate in this study entitled:
A Phase 1 Multicenter Study Evaluating the Safety and Potential Activity Of Two Escalating Doses of *h*Maxi-K Gene Transfer By Direct Injection into the Bladder Wall In Female Participants With Idiopathic (Nonneurogenic) Overactive Bladder Syndrome and Detrusor Overactivity: Double Blind, Imbalanced Placebo Controlled Design Within 2 Sequential Active Treatment Groups

I have read this Informed consent form and have had the opportunity to ask questions. The study doctor in charge of the study will inform me of any new findings during the course of this study that may affect my willingness to continue participation.

I authorize the release of my medical records to the sponsor Ion Channel Innovations, LLC, the Food and Drug administration, the Institutional Review Board, the Data Safety Monitoring Board, and foreign governmental drug approval agencies for purposes related to the study or the study drug.

I have been told that I will be given a signed and dated copy of this Consent Form
By signing this Consent Form, I have not given up any of the legal rights that I otherwise would have had as a participant in a research study.

_____
Name of Patient

_____
Patient's Signature Date Time

_____
Name of Individual Obtaining Consent

_____
Signature of Individual Obtaining Consent Date Time

Biomedical Research Alliance of New York LLC

Institution Name (use the parent institution, not the particular hospital)

Subject Information and Informed Consent Form

Protocol Title	A Phase 1Multicenter Study Evaluating the Safety and Potential Activity Of Two Escalating Doses of *h*Maxi-K Gene Transfer By Direct Injection into the Bladder Wall In Female Participants With Idiopathic (Non-Neurogenic) Overactive Bladder Syndrome and Detrusor Overactivity: Double Blind, Imbalanced Placebo Controlled Design Within 2 Sequential Active Treatment Groups
Protocol Number	ION 03-OAB
Sponsor	Ion Channel Innovations, LLC 969 Park Ave., 1G New York, NY 10028
Principal Investigator	**Principal Investigator Name**
Institution Address	**Principal Investigator Address**
Telephone	**Principal Investigator Telephone number**
24 Hour Telephone	**Principal Investigator 24 hour Emergency Telephone number**

PURPOSE OF THE SUBJECT INFORMATION AND CONSENT FORM
INTRODUCTION:
The purpose of this document is to inform you in writing of the purposes of this research, a description of the procedures to be followed, possible risks and discomforts, precautions and the basic ground rules which will govern this research study. Please, read this informed consent form and ask as many questions as you like.

The staff and your study doctor are available to talk about them. When you have completed reading, and if you decide to join in the study, you will be asked to initial and date each page and sign the last page. Your signature means that you have read and have also listened to a spoken explanation of the information to follow.

Please read this form carefully before you make your decision. You may refuse to participate in this study and this decision will not be held against you, nor will it change any matters between you and this office, and you will continue to receive the same medical care.

FINANCIAL DISCLOSURE
Ion Channel Innovations, LLC is providing funds to **Principal Investigator name** on a per subject basis for conducting this research study.

PURPOSE: NATURE AND PURPOSE OF THE STUDY
You are being asked to be a part of this research study because you have a condition called overactive bladder.

The purpose of this study is to evaluate the safety of a new product that uses human gene transfer called *h*Maxi- K when it is given to patients with overactive bladder. Human Gene transfer is a new type of therapy that is the process of placing genetic material (DNA or RNA) into a person. At present, human gene transfer is experimental and is being studied to see whether it could treat certain health problems by making proteins that treat the problem. Human gene transfer may help improve genetic disorders, (such as, sickle cell anemia, hemophilia, and cystic fibrosis). This type of experimentation is sometimes called "gene therapy" research.

*h*Maxi-K is a "naked," human cDNA. Compared to other gene therapies, hMaxi-K does not use viruses to make them effective. *h*Maxi-K does not correct a genetic defect. Instead, *h*Maxi-K cDNA produces a protein that is expected to cause smooth muscle cells to relax. *h*Maxi-K is injected directly into the bladder wall where the gene is available and taken up by the smooth muscle cells of the bladder. Two different dose levels of *h*Maxi-K will be studied, (16,000 and 24,000 microgram doses). You will receive 20 to 30 injections directly into your bladder wall of only one of these doses or Placebo (a solution containing no active drug- sugar and salt water solution). All of the women in the study will either be those who no longer have periods or cannot have children and have symptoms of overactive bladder that include:

- Frequent urination (that is, having to go to the bathroom more than 8 times per day);
- Symptoms of urinary urgency where you experience a sudden need to pass urine, which is difficult to hold back or the complaint of waking at night two or more times to urinate; and/or
- Urge urinary incontinence which is the complaint of leakage of urine that cannot be stopped accompanied by or immediately preceded by urgency on the average of 5 times per week.

This gene transfer product that you may receive is not approved by the Regulatory Authorities (the governmental agencies responsible for approving new drugs such as the Food and Drug Administration [FDA]) for use in treating your condition and is therefore considered to be experimental or "investigational."

Currently, there are several approved medications to treat overactive bladder including drugs (pills) such as: Detrol® (oxybutynin), Enablex® (darifenacin), VESIcare® (solifenacin), Ditropan® (tolterodine), Myrbetriq® (mirebegron) and Botox® (Botulinium Toxin A) by injection into the bladder wall. You are not permitted to use these drugs while you are in this study.

NUMBER OF SUBJECTS AND DURATION OF STUDY

Approximately 18 women will participate in this study. Each woman's participation in the study will last for up to 184 days (up to 7 months). You will have a total of 9 visits to the office and a telephone contact 1 day post dosing and 3 days post dosing to evaluate for any new complaints. If you are randomly assigned to receive hMaxi-K, you will be followed for an additional 18 months after the last study visit has completed. The office will contact you at 6 month intervals by phone to evaluate for any safety concerns.

During the study you will have to complete certain study-specific tests. Details about the study-specific tests, examinations, and questionnaires are included in this form.

DESCRIPTION OF THE RESEARCH STUDY

Study Medication:

Two different dose groups of *h*Maxi-K will be tested in this study: 16000 micrograms and 24000 micrograms. You could receive one of these 2 doses or also receive placebo (no active drug – sugar and salt water solution).

A total of up to 9 women will be enrolled in each dose group. For the 9 women per dose group, 6 will be randomly assigned *h*Maxi-K and 3 subjects randomly assigned placebo. The first 9 women will be assigned 16000 micrograms or placebo; the second 9 subjects will be assigned 24000 micrograms or placebo. That is, depending on which dose group you are in, you will be randomly assigned (like flipping a coin) to one of the 2 treatment groups (*h*Maxi-K or placebo). Your chance of getting *h*Maxi-K is approximately 2:1 or nearly two out of three.

Study Procedures:

Visit 1 (2 weeks prior to injection): If you agree to take part in this study, your study doctor will check whether or not you belong to the group of women that is eligible for the study. You will then undergo study specific tests, including a medical history, physical examination, a fasting blood sample test, urine tests, an electrocardiogram (ECG), and bladder scan to measure urine volume after you urinate using a wand that reflects sound waves over your abdomen). You will also be required to complete some questionnaires and diaries describing your condition and state of health. You will also be catheterized (a very small tube will be passed into your bladder) to collect a urine specimen to make sure you do not have any urinary tract infection.

Before you leave the clinic you will be scheduled for your second Screening visit which will occur within 6 days after visit 1. However, in some cases if scheduling permits you may have the procedures required at visit 1A performed at Visit 1(cystometry and urine cultures before and after cystometry). A cystometry is a procedure to test your bladder function and requires that a catheter (small narrow tube) be put into your bladder through your urethra (a canal that goes from your bladder to the outside of your body enabling you to urinate) and a small catheter will be placed into the rectum. Only if Visit 1A is scheduled on a separate day, you will be given a diary that you will need to complete for approximately 6 days or less prior to visit 1A to see if you are

completing the diaries correctly; a member of the study staff will be calling you to remind you to complete your diary. You will also be given a cylinder for urine measurement at home and instructed about using your pads. You will need to bring in a plastic bag, with all the pads you have worn for the 3 days prior to Visit 1A and a clean pad to use as a baseline. You will be instructed to not take any antiplatelet or non-steroidal anti-inflammatory drugs (such as aspirin, ibuprofen, naproxen, etc) and anticoagulant drugs (such as warfarin, Coumadin, heparin, etc) that may increase bleeding for at least 10 days prior Visit 2. All visit 1 study-specific tests will only be performed after you sign this informed consent form.

Visit 1A (14-8 days prior to injection):
Your study doctor will evaluate your visit 1 information and procedures to confirm your eligibility. Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit. Upon doing so, you will have a cystometry. As above, cystometry is a procedure to test your bladder function and requires that a catheter (small narrow tube) be put into your bladder through your urethra (a canal that goes from your bladder to the outside of your body enabling you to urinate) and a small catheter will be placed into the rectum. The cystometry will provide information that will help your doctor determine how your bladder function (how bad your overactive bladder condition is). In total, this procedure will last about 60 minutes.
Before you leave the clinic you will be scheduled for your next visit which will occur 8 days after this visit.
You will have some urine collected for culture and testing prior to the cystometry and following the procedure.
You will be given a diary that you will need to complete for 7 days prior to the next visit (visit 2); a member of the study staff will be calling you to remind you to complete your diary. You will also be given a cylinder for urine measurement at home and instructed about using your pads. You will need to bring in a plastic bag, with all the pads you have worn for the 3 days prior to Visit 2 and a clean pad to use as a baseline.
You will be instructed to not take any non-steroidal anti-inflammatory drugs (such as aspirin or ibuprofen, naproxen, etc) that may increase bleeding for at least 10 days prior Visit 2.
The results of all the procedures and questionnaires done at Screening Visit 1 and 1A, your completed patient 7 day diaries, and 3 days of used pads will be used at Visit 2 by your study doctor in the evaluation of your study participation.

Visit 2: (Baseline visit/Study injection)
Your study doctor will evaluate your visit 1 and 1A information and procedures to confirm your eligibility. Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit.
If you are eligible and agree to continue to be in the study, you will be asked questions about your health since the last visit, answer questions about how your overactive bladder condition affects your quality of life, have a physical examination (including a pelvic exam), urine specimen collected, blood drawn, blood pressure taken and an ECG (recording of the electrical activity of the heart using sensors placed on your chest) before giving you the study drug.

Administration of Study Drug. The drug will be given by 20 to 30 direct injections into the wall of your bladder after placement of a cystoscope (a very small telescope type instrument allowing the doctor to see the inside of your bladder). You will have a local anesthetic administered prior to the drug administration so hopefully the procedure should be relatively pain free.

After the drug is given to you, your blood pressure will be recorded every 15 minutes for the first 2 hours. You will be required to stay at the study site for at least 2 to 3 hours after dosing. You may be asked stay longer if your doctor believes it is necessary.
At 2 hours after dosing you will have blood drawn again to test for study drug levels. At discharge from the clinic you will also be asked to leave a urine specimen for testing to make sure you have no infections after the procedure and to test for study drug levels. You will be given an antibiotic to take on the day of visit 2 and for 2 days thereafter.
You will be given a diary that you will need to complete for 7 days prior to visit 3; a member of the study staff will be calling you to remind you to complete your diary. You will also be given a cylinder for urine measurement. You will need to bring in a plastic bag with any pads you have worn for the 3 days (and a clean pad to use as a baseline) prior to Visit 3, which will be 7 days after study injection.

1 and 3 Day Telephone Contact
On day 1 and 3 post injection, after you have received the study drug, someone from the office will give you a call at home to evaluate for assessment of adverse reactions and to see how you are doing. However if you have any problems or complaints at any time during the study you should call the office immediately. If you do have complaints, you may be asked to come for an unscheduled visit for further evaluation.

Visit 3: (8 days post injection)
During visit 3 you will have the following examinations: complete physical exam including vital signs (blood pressure, heart rate, and temperature), ECG, various fasting blood samples for routine analysis, and urine and blood samples to test if drug is still detectable in your urine or blood. Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit. You will be asked to complete various questionnaires to study any changes in how your overactive bladder condition affects your life.
You will be given a diary that you will need to complete for 7 days prior to visit 4; a member of the study staff will be calling you to remind you to complete your diary. You will also be given a cylinder for urine measurement. You will need to bring in a plastic bag with pads you have worn for the 3 days and a clean pad to use as a baseline (and a clean pad to use as a baseline) prior to the next visit.

Visits 4: (15 days post injection)
Two weeks after you were given the study drug you will return to the office with your completed patient diaries and all used pads worn for 3 days prior to this visit (and a clean pad to use as a baseline). Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit. At this visit you will have a physical examination and a bladder scan will be done, as well as collection of a fasting blood and urine samples. You will also have a physical examination, measurement of vital signs, and complete questionnaires. You will be given a diary that you will need to complete for 7 days prior to visit 5; a member of the study staff will be calling you to remind you to complete your diary. You will also receive a cylinder for urine measurement. You will need to bring in a plastic bag with any pads you have worn for the 3 days prior to the next visit (and a clean pad to use as a baseline).

Visit 5: (8 weeks post injection)
One month after you were given the study drug you will return to the office with your completed patient diaries and all used pads worn for 3 days prior to this visit (and a clean pad to use as a baseline). Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit. At this visit you will have a repeat

cystometry (as described above in Visit 1) performed to study your bladder muscle activity as well as a physical examination, vital signs, fasting blood and urine samples, and the completion of questionnaires. At discharge you will pass some urine for testing to make sure you have no infections after the catheter was removed.
You will be given a diary that you will need to complete for 7 days prior to visit 6; a member of the study staff will be calling you to remind you to complete your diary. You will also be given a cylinder for urine measurement. You will need to bring in a plastic bag with any pads you have worn for the 3 days prior to the next visit (and a clean pad to use as a baseline).

Visit 6 (8 weeks post injection):
Two months after you were given the study drug you will return to the office with your completed patient diaries and all used pads worn for 3 days prior to this visit (and a clean pad to use as a baseline). Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit. At this visit you will have your vital signs taken, bladder ultrasound conducted, urine and fasting blood samples collected to test if drug is still detectable in your urine or blood, and questionnaires will also be done. At discharge you will be given a diary that you will need to complete for 7 days prior to visit 7; a member of the study staff will be calling you to remind you to complete your diary. You will also be given a cylinder for urine measurement. You will need to bring in a plastic bag with any pads you have worn for the 3 days prior to the next visit (and a clean pad to use as a baseline).

Visit 7: (12 weeks post injection)
Three months after you were given the study drug you will return to the office with your completed patient diaries and all used pads worn for 3 days prior to this visit (and a clean pad to use as a baseline). Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit. At this visit you will have a physical examination, vital signs taken, fasting blood and urine samples will be obtained and questionnaires will also be done.

Visit 8: (24 weeks post injection)
Six months after you were given the study drug you will return to the office with your completed patient diaries and all used pads worn for 3 days prior to this visit (and a clean pad to use as a baseline). Your doctor will review your concomitant medications and perform an overall assessment of how you are feeling since your last visit. At this visit you will have a physical examination, ECG, a repeat cystometry (as described above in Visit 1A), a bladder scan to check for residual urine, your vital signs taken, fasting blood and urine samples collected, and questionnaires will also be done.
Following Visit 8, the study personnel will contact you for an additional 18 months (approximately every 6 months), to review any problems or complaints you may be have.
Blood and urine samples will be collected at various time points. Fasting blood will be collected up to 9 times during the study as described above for the different study visits. The total amount of blood to be drawn throughout the study (over 6 months) is approximately 115 ml that is equal to about 9 tablespoons. The samples will be sent to a laboratory contracted by your study doctor for analysis. The site staff may contact you before each scheduled visit to remind you to fast. You will be asked to not exercise or do strenuous activities prior to any blood sampling. Urine samples will also be collected up to 11 times during the study as described above. These urine samples, besides standard tests, will test for signs of urinary tract infection. Eight urine and 8 blood samples will also be taken to test for the presence of gene transfer product (study drug) throughout the visits. At Visit 2, you will have blood and urine samples taken twice to measure for the study drug - before dosing (at the same time as other blood and urine safety tests are taken) and again at 2 hours after dosing. At Visits 3 to 8, blood and urine samples to test for

study drug will be taken only once when blood and urine are collected for other safety tests. During the 18 month follow-up, if there is any hMaxi-K gene still measured in your blood or urine at Visit 8, then at least 2 additional consecutive ~~weekly~~ monthly samples of blood and/or urine will be taken until there is no more evidence of the gene.
At each visit you will be asked about your medications and any changes to your health since receiving the study injection. You must tell the clinic personnel of any changes to or additions to your regular medications.

There may be reasons why you cannot participate in this study. The study doctor or study staff will discuss these reasons with you.

RISKS AND DISCOMFORTS
You must understand that there may be risks to you while you a part of this study. Your medical condition may not improve or may worsen while you are part of the study. As with any investigational drug, it is possible that you may experience some discomfort or adverse reactions (side effects) associated with the use of the drug that are not known prior to this study.

Possible Risks with *h*Maxi-K:
A study looking at the safety and effects of *h*Maxi-K in 20 men with impotence has been completed. Although *h*Maxi-K was given in a different organ in this study (injected into a blood vessel in the penis), few adverse events were seen and few were thought to be due to the gene transfer product (see the next section). In addition a study evaluating the active drug in 16 women with overactive bladder such as you have has been completed. As with any investigational drug, there remains potential risk for adverse effects after a gene product is given that changes the flow of water and salts (which is how *h*Maxi-K works). Any organ whose function could be affected by a change in the flow of water and salts could have bad effects after the injection of *h*Maxi-K, such as blood vessels and the brain. There could be local effects in the bladder from the catheter or the solution such as infection, local pain, or irritation. There could possibly be some bleeding from the injections and blood in the urine after the procedure. An objective group of doctors called the Data Safety Monitoring Board will also be reviewing all the data that comes from this study to ensure that any problems are addressed quickly and to advise the clinic if it is necessary to stop the administration of the drug.

Administration of *h*Maxi-K in humans has shown that the drug is well tolerated with few side effects reported. To date, as above, a total of 20 men have been given *h*Maxi-K in a trial for impotence; three men have received 500 micrograms, three received 1000 micrograms, three men received 5000 micrograms, two men have received 7500 micrograms, three men received 8000, three men received 12000 micrograms, and three men received 16000 micrograms (the lowest dose in the study you are taking part in). In these men only one of the events was considered related to the study drug, *h*Maxi-K, and was reported by one of the men who received 12000 micrograms as a tingling warmth in the penis.
Other adverse events that were reported but **considered unrelated** to the study drug, *h*Maxi-K included the following:
Heart arrhythmia (abnormal heart rhythm),, Kidney stones , Acid reflux, Sciatic pain (pain that runs down the back of leg), Upper respiratory infection, Parasitic intestinal infection, Foot swelling, Flu like symptoms, Hand pain, Platelet changes, Common cold, Brief penile pain.
In the female participants for the overactive bladder study ten participants received the 5000 microgram dose (7 in this group completed the study; 3 discontinued early seeking other treatment for their overactive bladder symptoms), 6 participants received the 10000 microgram dose and 5 participants received placebo (all participants completed in the 10000 microgram and

placebo groups). There were no serious adverse events reported or a withdrawal for an adverse event.
In the 5000 microgram dose, **possibly related** adverse events were reported in one subject each, and included urinary tract infection, a heart block (abnormal heart rhythm, fatigue, headache, shaking chills, and insomnia.
Unrelated events were reported and included headache; rash; fractured left (big) toe; infection left (big) toe; worsening of fat tissue near the vagina; knee tendonitis; right kidney cyst benign; worsening of depression; worsening of acid reflux/indigestion; elevated blood creatinine (lab test for kidney function); diffuse loss of renal parenchyma (kidney tissue); hypertensive renal disease; atypical chest pain; CK and CK-MB elevated (lab tests possibly secondary to high blood pressure caused by kidney disease) diarrhea; vomiting, hiatal hernia; bacteriuria (bacteria in the urine); constipation; fatigue; fall; upper lip skin scrape secondary to fall; acne on face; and urinary tract infection.
In the 10000 microgram dose group, adverse events were all considered **unrelated** and included in one subject each common cold; elevated blood pressure; worsening of urge incontinence; tension headache; low back pain; fall; pain on urination (dysuria); elevated liver function tests; and hepatitis C.
In the **placebo** group, heart palpitations were reported in one participant, which were considered **possibly related**, mild severity, and occurred 6 days post treatment. **Unrelated events** for placebo that were reported in one participant each included slight irritation at the vulva, fractured pelvis (left side) and wrist fracture (left); 4 unrelated urinary tract infections (UTIs) were reported in 2 participants.
No clinically significant changes were seen in the physical examinations or laboratory values during the study (except for those changes in laboratory tests mentioned above in one participant who received 5000 micrograms
and in one participant who received 10000 micrograms which were considered unrelated to study gene transfer). *h*Maxi-K is a unique therapy and therefore there are no similar drugs for comparison of side effects. As with any investigational drug, there is a possibility of unknown side effects.
Also as with any drug, there is a potential for an allergic reaction. Since *h*Maxi-K is a foreign substance to the body, the body may produce antibodies (protein produced by the body to neutralize or destroy foreign substances in the body) against *h*Maxi-K which can possibly lead to allergic reactions. Allergic signs may also occur from other compounds, such as those in the placebo, in certain individuals. Therefore, please notify your study doctor immediately if you experience itching, rash, nausea, fever or other signs.
Pregnant patients (or a patient who could get pregnant) are excluded from the study. The safety of *h*Maxi-K in pregnant and/or nursing women has not been established. Therefore only women who are postmenopausal or who have had surgical sterilization (hysterectomy, tubal ligation) will be allowed in the study. It is extremely important to tell your study doctor if you are pregnant, are still able to become pregnant, or become pregnant during the course of this study.
Laboratory tests suggest that *h*Maxi-K breaks down or disintegrates if it is in the urine longer than 30 minutes.
However, there is the risk that you could still pass some gene transfer product in your urine. You are asked to not have sexual intercourse for the first 24 hours after *h*Maxi-K is put into your bladder.

Risks of Cystometry
Insertion of a bladder catheter into the bladder has some minimal risks. They include urinary tract infection and irritation. Your urine will be collected to test for any infections and you will be treated with appropriate antibiotics if they occur.

Risks of Cystoscopy:
Insertion of a cystoscope into the bladder has some minimal risks. They include urinary tract infection and irritation. There also may also be some slight blood in the urine after injection of the drug into your bladder wall. Bleeding following injection at a puncture site is not uncommon. Your urine will be collected to test for any infections and you will be treated with appropriate antibiotics if they occur.

Risks of Blood Draws:
Possible side effects from blood drawing include: faintness, inflammation (redness and swelling) of the vein, pain, bruising, bleeding at the site of puncture, and a slight possibility of infection at the site of the needle stick.
Medical supervision will be provided throughout the study. If indicated, you will be treated appropriately for any adverse reaction should such occur. If you experience any side effects or research-related injury, contact:
Principal Investigator name and telephone number

Potential Benefits:
The reason for doing this study is to test the safety of different doses of *h*Maxi-K given by injection in participants with overactive bladder syndrome. Although there is no human experience that gene transfer injections could help improve the function of the bladder for some participants there are animal data that indicate that *h*Maxi-K might have a potentially beneficial effect on people experiencing urgency. You may not benefit from being in this research study. However, the information learned from this study may, benefit other people with this condition in the future. You will not have access to the study drug after the study.

ALTERNATE THERAPY
*h*Maxi-K is a unique therapy and therefore there are no similar drugs for comparison. Common side effects of other drugs used to treat overactive bladder include dry mouth, dry eye, thinking problems, memory loss and constipation. These other drugs which are given as pills include Detrol® (tolterodine) and Ditropan XL® (oxybutynin), Enablex® (darifenacin), Vesicare® (solifenacin), Sanctura® (tospium) and Myrbetriq® (mirebegron). In addition, Botox® (Botulinium Toxin A) is a drug given by injections into the bladder wall to inhibit bladder contractions. Botox® (Botulinium Toxin A) is associated with urinary retention where you are unable to urinate and therefore need a catheter placed into your bladder for possibly a long duration.

NEW FINDINGS
Any new findings that develop or are reported by the Sponsor during the research that might change your mind about continuing to take part in this study will be provided to you as they become available.

COST
All study medication and study-related procedures will be provided at no cost to you for your participation in this study. There will be no additional costs to you for taking part in this study.

PAYMENT FOR PARTICIPATION
You will be ~~paid~~ reimbursed ~~a total amount of up to $ (insert total~~[m1] ~~amount to be paid to participant and complete table below)~~ for your participation in this study. For details, refer to the payment schedule below:

Study Visit Amount Form of payment (cash/check)

Study Visit	Amount
Visit 1/1A- Screening	$
Visit 2 - Baseline	$
Telephone Follow/up	$
Visit 3 – Week 1	$
Visit 4 – Week 2	$
Visit 5 – Week 4	$
Visit 6 – Week 8	$
Visit 7 – Week 12	$
Visit 8 – Week 24	$
Telephone Follow-up	$
~~**Total**~~	~~**$**~~
	Additional $ /visit to test for study drug or other unscheduled visit repeat assessments

Should you discontinue the study for any reason you will be paid for the time you have been in the study.

SUBJECT RESPONSIBILITIES

As a subject in this research study, it is expected that you will carefully follow the instructions of the doctor and staff. You are expected to:

- Read this Subject Information and Consent Form and ask as many questions as needed.
- Provide the study doctor with a complete history of illnesses (and medications) you've had in the past.
- Provide the study doctor with the name, address, and phone number of your current regular doctor, and state whether or not the study doctor can contact your regular doctor about your being in this study and request your medical records from him/her.
- Keep to the schedule of visits and, if there is a problem, call the study staff to reschedule.
- Complete all tests, procedures, and questionnaires to the best of your ability.
- Report any symptoms/side effects you may be experiencing to the study doctor.
- Inform the study doctor or study staff of any drugs you may have taken between visits.
- Ask questions during the study about anything that may concern you.
- Do not take medications that the study doctor has asked you not to take while participating in the study.
- Do not donate blood while you are participating in the study and for at least one month after you have completed the study.

COMPENSATION FOR RESEARCH-RELATED INJURY

You may be exposed to risk of injury from participation in this study. If injury occurs, all available treatment choices will be considered and given to you by the investigator. In the event

of any physical and/or medical injury resulting from your participation in this research project, the Sponsor (Ion Channel Innovations, LLC) will pay medical expenses for any medical problems caused by the study procedures or study drug provided that the study drug was given as directed by your study doctor and/or study staff, and only if the costs are not covered by your medical or hospital insurance or by third party or governmental programs. No additional payments will be available. You must follow the directions of the study doctor and/or study staff to be eligible for this coverage. There is no provision for payment for medical care or for monetary payment from (**Name of Principal Investigator's institution**) for any study-related injury. No other compensation will be offered by ION Channel Innovations, LLC or institution or the Biomedical Research Alliance of New York.

LEGAL RIGHTS

By signing this form, you have not given up any of the legal rights that you otherwise would have been entitled to as a participant in a research study.

CONFIDENTIALITY

The study doctor and staff will collect information about you during the study that will be entered into a database. Your name will not be in the database, but your data will be assigned a specific subject number.

To the extent allowed by law, every effort will be made to keep your personal information confidential.

However, information from this study will be submitted to the study sponsor and to the U.S. Food and Drug Administration (FDA). It may be submitted to governmental agencies in other countries where the study drug may be considered for approval. Medical records, which identify you and the consent form signed by you, will be looked at by the sponsor or the sponsor's representatives and may be looked at by the FDA and other regulatory agencies, the Institutional Review Board, and the Biomedical Research Alliance of New York.

While these parties are aware of the need to keep your information confidential, total confidentiality cannot be guaranteed. The results of this research project may be presented at meetings or in publications; however, you will not be identified in these presentations and/ or publications.

A description of this clinical trial will be available on *www.ClinicalTrials.gov*, as required by U.S. ~~law~~ Law[m2].

This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

AUTHORIZATION TO USE AND DISCLOSE PERSONAL HEALTH INFORMATION

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify you. If you choose to be in this study, the study doctor will get personal information about you. This may include information that might identify you. The study doctor may also get information about your health, including:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Information obtained during this research about laboratory test results
- Results from diagnostic and medical procedures including but not limited to X-rays, physical examinations and medical history

- Billing records
- Information about your health may be used and given to others by the study doctor and staff. They might see the research information during and after the study.
- Your information may be given to the sponsor of this research. “Sponsor” includes any persons or companies that are working for or with the sponsor (Ion Channel Innovations, LLC), or are owned by the sponsor. Information about you and your health which might identify you may be given to:
- The U.S. Food and Drug Administration
- Department of Health and Human Services agencies
- Governmental agencies in other countries
- Biomedical Research Alliance of New York (BRANY)
- The Institutional Review Board
- Accrediting agencies
- Data Safety Monitoring Boards
- Health Insurers/Payors

Your personal health information may be further shared by the groups above. If shared by them, the information will no longer be covered by the U.S. federal privacy laws. However, these groups are committed to keeping your personal health information confidential. If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others without your permission.

Information about you and your health that might identify you may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done, and they will be reviewing your information for this purpose. The information may be given to the FDA. It may also be given to governmental agencies in other countries. This is done so the sponsor can receive marketing approval for new products resulting from this research. The information may also be used to meet the reporting requirements of governmental agencies.

This authorization does not have an expiration date. If you do not withdraw this authorization in writing, it will remain in effect indefinitely.

By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. You do not have to sign this consent form. If you choose not to sign this consent form, you will not be able to be in this research study. Your decision not to sign this consent form will not have any effect on your medical care and you will not lose any benefits or legal rights to which you are entitled.

You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you may not be allowed to look at or copy your information until after the research is completed.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor at the address on the front of this informed consent form. If you withdraw your permission, you will not be able to continue being in this study, but you will not have any penalty or loss of access to treatment or other benefits to which you are entitled. When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Notice Concerning HIV-Related Information: The recipients of HIV-related information are prohibited from redisclosing it without your authorization unless permitted to do so under federal or state law. You also have a right to request a list of people who may receive or use your HIV-

related information without authorization. If you experience discrimination because of the release or disclosure of HIV-related information, you may contact the New York State Division of Human Rights at 212-480-2493 or the New York City Commission on Human Rights at 212-306-7450. These agencies are responsible for protecting your rights. Because this study involves gene transfer, safety information must be reported to the Recombinant DNA Advisory Committee of the National Institutes of Health (NIH) and Institutional Bio-safety Committee (IBC), a group of scientist and non-scientists who review the study in accordance with NIH guidelines. This information is available to the public. However, no information by which participants can be identified will be reported with the safety information.

VOLUNTARY PARTICIPATION
Your decision whether or not to take part in this research study is completely up to you. There will be no penalty or loss of benefits to you if you decide not to participate. In addition, you may withdraw from this study at any time for any reason. There will be no penalty if you decide to withdraw. Should you decide to stop being a part of this study, you must notify your study doctor that you wish to withdraw. If you decide to withdraw, it will be necessary for you to return to the study center for a final visit. This will assist your study doctor in determining if you have any continuing medical problems. You can also discuss with your study doctor how to best continue your medical care.

WITHDRAWAL
The study doctor, the Sponsor company, and the FDA have the right to stop the study or your participation in it at any time, with or without your consent, for any reason, including the following: if you have a side effect from the study drugs; if you need a treatment not allowed in this study; if you do not keep appointments; if you do not take the study drug as instructed; or if the study is canceled by the FDA or the Sponsor company.

QUESTIONS
You have the right to ask questions concerning the possible risks of this study at any time. You will be told of any safety information related to the study or study drug.
If you have questions about the study or experience any research-related injury, contact:
Principal Investigator or his/her associates: **Principal Investigator name**

Telephone Number(s): M-F: Principal Investigator telephone number (day and after hours)
If you have questions about your rights as a research subject, you may contact the IRB at: (516) 470-6900.

SUBJECT'S STATEMENT OF CONSENT
I voluntarily agree to participate in this study entitled:
A Phase 1 Multicenter Study Evaluating the Safety and Potential Activity Of Two Escalating Doses of *h*Maxi-K Gene Transfer By Direct Injection into the Bladder Wall In Female Participants With Idiopathic (Nonneurogenic) Overactive Bladder Syndrome and Detrusor Overactivity: Double Blind, Imbalanced Placebo Controlled Design Within 2 Sequential Active Treatment Groups

I have read this Informed consent form and have had the opportunity to ask questions. The study doctor in charge of the study will inform me of any new findings during the course of this study that may affect my willingness to continue participation.

I authorize the release of my medical records to the sponsor Ion Channel Innovations, LLC, the Food and Drug administration, the Institutional Review Board, the Data Safety Monitoring

Board, and foreign governmental drug approval agencies for purposes related to the study or the study drug.

I have been told that I will be given a signed and dated copy of this Consent Form
By signing this Consent Form, I have not given up any of the legal rights that I otherwise would have had as a participant in a research study.

_____
Name of Patient

_____
Patient's Signature Date Time

_____
Name of Individual Obtaining Consent

_____
Signature of Individual Obtaining Consent Date Time