Title of Study: "Randomized Controlled Trial of PTNS versus Sham Efficacy in Treatment of Bladder Pain Syndrome."

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Study Number: s15-01447

- **PURPOSE OF THE STUDY AND BACKGROUND –**

    - Our primary aim in this pilot study is to evaluate the efficacy of the systematic effects of posterior tibial nerve stimulation (PTNS) treatment compared to an inactive sham intervention in female subjects with interstitial cystitis/bladder pain syndrome (IC/BPS) in an intent-to-treat analysis. Our primary outcome measure will be the Patient Global Impression of Improvement (PGI-I) a single item questionnaire assessing overall impression of improvement over time at the initial 12 weeks endpoint.

    - Our secondary outcomes will include change from baseline in SF-12 quality of life scores, Visual Analog Scale (VAS) and O'Leary –Sant pain scores at 12 weeks To confirm the validity of the sham, subjects will be asked to identify which intervention they believed they received during the study at study conclusion. Additionally subjects will be presented with OAB-Q short forms. This will allow for evaluation of subjects with concomitant overactive bladder and painful bladder syndrome characteristics.

    - We hypothesize that subjects randomized to the PTNS arm will demonstrate a greater improvement in both pain and quality of life scores, when compared with subjects who are randomized to the sham arm. Additionally, we hypothesize that the validity of the inactive sham intervention will be appropriately confirmed in our study population.

- **Background:**
- Bladder Pain Syndrome (BPS), which includes the sub-variant of interstitial cystitis (IC), is defined as "an unpleasant sensation (pain, pressure, discomfort) perceived to be related

to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes"(1). Characteristically, it is pain lasting longer than 6 months, which is often refractory to treatment. BPS significantly impairs function of daily activities and is associated with decreasing ability to perform activities of daily living (1,2). A complete medical history including urinary and bowel symptoms, history of reproductive tract disease, psychoneurological disorders and musculoskeletal syndromes is key in patients who suffer from this disorder (6). It is important to consider psychological and social factors associated with BPS, in addition to possible physical causes. BPS is a diagnosis of exclusion and the symptoms cited are variable and have a wide-range. Additionally the etiology of this disease is unknown, making the development of directed therapies a challenge. BPS affects approximately 4.3% of patients in the United States who are seen in a primary care setting(3). The overall healthcare costs for women with a diagnosis of BPS are more than twice that of age matched controls. A woman with a diagnosis of BPS is expected to incur a mean cost of $6,614 a year, including $1,572 for medications and $3,463 for outpatient medical services (4,5). The adverse effects on a patient's quality of life can be severe, and are similar to those reported for other chronic diseases such as congestive heart failure, Crohn's disease and diabetes mellitus (5).

- How to effectively treat IC/BPS has remained a major challenge. Despite multiple modalities used to treat this syndrome including antihistamines, antidepressants, local anesthetics, neuromodulation, dietary and behavioral modifications and rarely surgery, many patients experience only short-term relief from these treatments and a large cohort of patients are refractory to these treatment options and resort to using a combination of therapies (5). In a recent Gallop poll of 5,325 US women concerning generalized pelvic pain, 11% of those polled limited their home activity, 11.9% limited their sexual activity, 15.8% took medication, and 3.9% missed at least 1 day of work per month due to the condition (6). The true incidence and prevalence of BPS are unknown due to the difficulty of diagnosis, however pelvic pain is a common problem encountered in the healthcare field and this poll reveals that currently available treatments do not adequately manage patient symptoms.

- Posterior tibial nerve stimulation (PTNS) is a minimally invasive method of neuromodulation, originating from traditional Chinese medicine. The technique identifies an acupuncture point that lies over the tibial nerve, and this point together with points at sacral and pubic sites have been used to treat pelvic disorders. McGuire and colleagues first tested this point as treatment for detrusor instability and found a decline in urinary urgency symptoms in this patient population (7,8). Since then,

multiple other trials have studied PTNS as a potential treatment for overactive bladder (OAB), chronic prostatitis, fecal incontinence, bladder pain syndromes or sexual dysfunction (9-12). PTNS has also been tested as a method to manage generalized pelvic pain, and favorable results have been demonstrated (13-15). To date, however, there is a paucity of robust literature on PTNS treatment for bladder pain specifically, and currently there are no randomized controlled trials comparing long-term effects of PTNS with control group. An evaluation of the literature revealed that more studies are required to understand the potential role for PTNS in the treatment of BPS (16). A sham PTNS model was recently validated as a mode to help identify the true efficacy of PTNS on overactive bladder and other disorders. Peters and colleagues found that patients were unable to identify the sham model correctly, resulting in a validated model to use when comparing PTNS treatment to placebo (17). There are few studies in the literature comparing PTNS to sham. One study revealed that PTNS is superior in the OAB population when compared with sham, however there is a paucity of data looking at the placebo effect in neuromodulation therapies in general and how this can specifically affect PTNS results (18-19). Additionally, there have been no trials looking at PTNS versus placebo for the treatment of BPS. Given the high rate of efficacy of placebo in pain syndromes, the lack of robust randomized controlled trials in this area inhibits our ability to understand whether PTNS is truly an effective treatment for BPS.

- *Innovation:*
- There are currently multiple accepted treatment methods for BPS. Recently, in addition to medical therapies, neuromodulation techniques have been described for treatment of bladder pain, both in the form of percutaneous nerve stimulation (PTNS) and sacral neuromodulation (SNM). Both of these techniques are FDA approved treatments for other pelvic floor disorders such as OAB and fecal incontinence. While there is some literature to suggest that SNM therapies are associated with higher rates of efficacy, this therapy is more invasive when compared to PTNS and has been associated with significantly higher costs.

- In addition to the aforementioned PTNS trials, there have been some reports on the benefit of SNM treatments, although the data is sparse and there are no direct comparisons of SNM with PTNS for the management of bladder pain (20-21). It seems imperative that we continue to study the effects of PTNS on bladder pain, so we can better understand the role of this treatment for our patients, and better recognize the characteristics of the patient population that would obtain the greatest benefit. Furthermore, once the efficacy of PTNS is better defined, a future direction comparing different modes of neuromodulation to assess presence of superiority in treatment

could be undertaken. The estimated cost of PTNS is approximately $1,800 for 12 sessions, which is the approved number of sessions currently outlined in the FDA usage of PTNS for other pelvic floor disorders. In contrast, the cost of sacral nerve stimulation is significantly higher. A recent study comparing costs of neuromodulation therapies for OAB revealed that cost after completing initial therapy with PTNS was $4867.00 while completion of SNM implantation and initial treatment cost an average of $24,342.00. Additionally, it was found that both methods had high levels of adherence, reaching 71% and 90%, respectively, however data revealed an incremental cost-effectiveness ratio of $99,872 in favor of PTNS (22). The proposed study can provide critical data to build cost-effectiveness models that will help answer important questions as health care resources become more limited. PTNS, if proven effective for treatment of bladder pain syndromes, could improve quality of life for many of the approximately 7 million women in the United States who are affected by bladder pain. Cost-effectiveness data may lead to savings that are significant to the healthcare system. A longer term look at the persistence of treatment will factor into this model as many patients with bladder pain are involved in a clinical paradigm, which includes multiple office and emergency room visits due to titration of analgesic interventions, etc. If PTNS proves to be an efficacious and has medium and long-term benefit for the treatment for BPS, this could result in even more cost savings for the healthcare system and the patient. This study is the first step to an accurate cost-analysis study in BPS.

- **Study Design**: This is a prospective, single center, double-blind, randomized, controlled trial comparing the efficacy of percutaneous tibial nerve stimulation to sham in the treatment of Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) through 12 weeks of therapy.
- **Investigational Device :** The device used will be the NURO™ Neuromodulation system, Medtronic Device Model # 3533, which is a non-implanted peripheral electrical continence device. The NURO neuromodulation system (stimulator model NURO 100) is currently FDA approved for use to treat patients with overactive bladder (OAB) and associated symptoms of urinary urgency, urinary frequency and urgency incontinence. As described previously in this document PTNS is widely used as an efficacious treatment for patients with lower urinary tract symptoms. It provides a minimally invasive alternative to sacral neuromodulation as it modulates the innervation of the bladder, urinary sphincter and pelvic floor peripherally. Given this, and the fact that many patients with bladder pain syndrome (BPS) have concomitant symptoms of urgency/frequency, it is reasonable to investigate the use of this product for treatment of bladder pain syndrome. While this has been described as a tool used for both BPS and chronic pelvic pain syndromes, there is a paucity of literature looking at this treatment

for these specific indications and more data needs to be collected (23). This device is of Non-significant risk due to the following:

- This device is not implanted and is not represented to be for use supporting or sustaining human life.
- While the device is for a use of substantial importance in treating disease there have been no previous studies identifying serious risk to the health, safety or welfare of a subject. Based on three randomized trials and one long term durability trial using PTNS, the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom issued guidance about this treatment technique stating "PTNS for OAB demonstrates effectiveness without major safety concerns"(24). The use of PTNS for Bladder Pain syndrome would be effectively the same use of the device, simply for another lower urinary tract symptom, bladder pain instead of overactive bladder. As discussed previously these symptom profiles often overlap in the community. In the previous studies using PTNS for bladder pain, no major adverse events were reported (18, 19, 24).
- Adverse events associated with PTNS are reported as mild, transient and relatively uncommon and include bruising and/or bleeding at the needle site and tingling or mild pain at the needle site. These adverse events have been documented at an incidence of 1-2% (18,25). These adverse events are much more favorable than those of sacral neuromodulation, which is a current off-label treatment used for bladder pain syndrome. Adverse events for sacral neuromodulation include pain at implant site, lead migration and infection, to name a few, with incidence rates of 5-15% (24-26).
- It is not purported or represented to be for use supporting or sustaining human life
- While it is desired that this device can be integral in providing improvement of symptoms, it is not used of substantial importance in diagnosing, curing, mitigating, or treating disease,

- **CHARACTERISTICS OF THE RESEARCH POPULATION**
  - **Number of subjects**: We aim to enroll 100 subjects in our study. Patients presenting to NYU Center for Female Pelvic Medicine and meet the inclusion criteria for the study will be recruited to participate in the study.
  - **Gender of Subjects**: BPS/IC is a condition found predominantly in women and thus only female subjects will be recruited.
  - **Age of subjects**: Subjects over the age of 18 will be recruited for the study. BPS/IC is a condition that generally does not afflict children and therefore they would be inappropriate to include in our study population.
  - **Racial and Ethnic Origin**: There are no enrollment restrictions based upon race or ethnic origin for this study. All subjects meeting the inclusion criteria for the study

will be approached. The patient population of the NYU Center for Female Pelvic Medicine come from diverse backgrounds. BPS/IC is a condition that disproportionately affects Caucasian women over Hispanic or African American women (ref) and the racial makeup of our patient population reflects this.

- **Inclusion Criteria**:
  - Women ≥ 18 years old with visual analog scale > 5
  - Cessation of all analgesics or other medication for pain for at least 2 weeks prior the PTNS intervention
  - Discontinuation of any other electrical stimulation methods 3 months prior to PTNS intervention
  - Capable of giving informed consent
  - Ambulatory
  - Capable and willing to follow all study-relation procedures

- **Exclusion Criteria:**
  - Patients pregnant or planning to become pregnant during the study duration
  - Botox use in pelvic floor muscles within the last year
  - Current urinary or vaginal infections
  - Current use of Interstim device
  - History of a cardiac pacemaker
  - Diagnosis of neuropathy

- **Vulnerable Subjects**: No vulnerable subject populations based on federal regulations are included in this trial. Children and fetuses are not affected by this disease, pregnant women are not PTNS candidates, and prisoners are not treated at the study site. The elderly are a potential, albeit likely small proportion of the patients with the diagnosis of BPS, thus they need to be included in our study population to make the results useful in clinical practice. They will be included in our study; however those who are no longer able to provide consent for themselves will be excluded.

- **METHODS AND PROCEEDURES**
  - **Methods and Procedures:**
- *Approach:*
- All patients seen at New York University Center for Female Pelvic Medicine to in the Department of Urology who suffer from BPS/IC, as defined above, will be offered

participation in this prospective randomized controlled study.

- Inclusion criteria will include: women ≥ 18 years old with visual analog scale > 5, cessation of all analgesics or other medication for pain for at least 2 weeks prior the PTNS intervention, discontinuation of any other electrical stimulation methods 3 months prior to PTNS intervention, capable of giving informed consent, ambulatory, capable and willing to follow all study-relation procedures.
- Exclusion criteria will include patients pregnant or planning to become pregnant during the study duration, Botox use in pelvic floor muscles within the last year, current urinary or vaginal infections, current use of Interstim, history of a cardiac pacemaker, diagnosis of neuropathy.
- Randomization will be carried out using computer-generated random allocations. A computerized random number generator will be used to generate a number 1-100. All odd numbers will be randomized to PTNS arm and all even numbers will be randomized to sham arm. This number will be generated by a co-investigator who is not involved in the consent process. He or she will provide an envelope revealing the randomization result to the investigator who is consenting the subject. Institutional Review Board approval from the NYU IRB will be obtained prior to starting the study.

- On-site training of investigators and research staff will include a study protocol lecture, demonstration of blinding apparatus setup, use of a standard PTNS system (needle, grounding pad and energy source) according to manufacturer instructions for use, and use of a TENS unit and placebo needles (for sham subjects). Subjects and study coordinators who will administer questionnaires will be blinded to the assigned treatment intervention throughout the trial. All subjects will be randomized 1:1 at the first intervention visit to PTNS or sham using a random block design. During the intervention session subjects will be in a comfortable seated position and lower extremities will be blocked and draped from view. All subjects will have three electrode pads placed to standardize the perception of the intervention between the 2 treatment arms. Next, instead of the inactive grounding pad used on the PTNS leg, the sham subjects will have an active adhesive pad placed on the bottom of the foot just below the smallest toe. This spot was chosen, as described in sham validation (17) since it is not part of the acupressure or acupuncture nerve pathway connected to the bladder, pelvis or any major organs. All subjects will be informed that they may or may not feel a sensory stimulus effect on their lower extremities as a result of the intervention. Subjects in both study groups will receive 12 weekly 30-minute intervention sessions and will be queried about adverse events. Evaluation of primary end point will be done on a weekly basis. Every two weeks the individual response to this parameter will be

assessed. Additionally, the overall change in primary endpoint will be evaluated at week 12. The secondary endpoints will be evaluated at week 12 as well. There will be a debriefing at week 12 after the study has been completed, to reveal to the subject which arm they were in.

- **PTNS group:**
    - The medial aspect of the lower extremity will be palpated and a needle insertion site will be identified approximately 5 cm cephalad from the medial malleolus and slightly posterior to the tibia. Between the posterior margin of the tibia and the soleus muscle, a 34-gauge acupuncture-like needle will be inserted approximately 3–4 cm deep to the tibial nerve. An adhesive grounding pad will be placed on the bottom of the foot just below the smallest toe. An inactive adhesive grounding pad will be placed on the top of the foot just above the small toe to be consistent with the sham pad placement. The needle and grounding pad will be connected to the stimulator and the stimulation will be increased from 0 to 10 mA as tolerated. Flexion of the greater toe and sensory stimulation in the bottom of the foot will be used to confirm proper needle placement. The needle will be taped in place. The electrical current will be set at an intensity that is well tolerated by the subject and the mA will be recorded on a subject report form. A 30-minute stimulation session will be given at 20 Hz. At the end of the procedure, the needle and grounding pad will be removed and discarded.

- **Sham group:**
    - The medial aspect of the lower extremity will be palpated and a needle insertion site will be identified approximately 5 cm cephalad from the medial malleolus and slightly posterior to the tibia. Between the posterior margin of the tibia and the soleus muscle a sham needle will be used at the tibial nerve insertion site. This will stimulate needle placement without puncturing the skin. The needle will be taped in place, similar to the PTNS procedure. The “grounding pad” from the TENS unit device will be placed on the bottom of the foot just below the smallest toe. Another gel electrode will be placed on the top of the foot just above the small toe for conduction. The TENS electrode will be connected by lead wires to the TENS unit, set at 20 Hz (as in the PTNS group). The TENS unit will then be turned on and the stimulation will be increased tot the subject’s first sensory level. At the time the subject senses localized stimulation to either the bottom of the foot or the toe the TENS unit will be left on for a 30 minute test period. The TENS unit will then be removed and the needle will be removed and discarded.

- Sessions for both groups will be performed once per week for 30 minutes. The total treatment period will be 12 weeks. All patients will undergo thorough evaluation for bladder pain through a detailed history and physical exam (both general physical and gynecologic). Baseline characteristics will be collected. At the baseline of the study and at completion of the 12-week treatment all patients still enrolled will be asked to fill out general and disease-specific pain and quality of life questionnaires. We will use VAS and the O'Leary-Sant scores to determine pain intensity, location of pain and associated symptoms. The OAB-Q will be used to identify characteristic features of associated bladder pain and OAB symptoms. The SF-12 scale will be used to evaluate quality of life of each subject at the three analysis intervals. Patient Global Impression of Improvement (PGI-I), a single item questionnaire assessing overall impression of improvement over time, will be administered at the initial visit and each visit thereafter up through the 12 weeks endpoint. This will allow us to assess progress of the primary end-point week-by-week and overall from baseline to end of treatment. Additionally we will perform an analysis of analgesia use and other past treatments used for pain in this population.

- Full disclosure of research proposal and description of the two possible arms of randomization will be conducted with all participants in the form of both written and verbal communication. Our goal is to conduct this study at NYU Hospital and this will ensure a wide catchment area, including women of various ages, ethnic groups and socioeconomic backgrounds. No subject will be excluded based on race, age or ethnicity. Subjects will also have opportunities throughout the trial to voice any concerns regarding the study and all human subjects will be protected from foreseeable research risks, as this trial will undergo IRB approval prior to initial execution.

    - **Data Analysis and Data Monitoring.**

        - The interventions applied in this study represent minimal risks to our subjects. Therefore a data monitoring committee will not be employed to monitor subject safety. The twelve (12) 30-minute PTNS sessions makes up the interventional portion of this study. There are no expected complications from a twelve (12) week PTNS treatment regimen beyond mild patient discomfort or mild bruising at the needle insertion site. The data that will be collected as part of the data safety monitoring plan will revolve around the PTNS and sham treatment sessions and patient experience with the PTNS and sham treatments. All data gathered beyond the PTNS vs Sham trial is purely observational. Patients

requesting to be removed from the study early and patient reports of pain associated with the treatments will be taken note of. Dominique Malacarne will be responsible for monitoring the data. Dr. Malacarne is the primary contact for subjects and thus she will be aware of unanticipated problems and any adverse events as they occur. After each 10 patients are enrolled, Dr. Brucker and Dr. Malacarne will review any adverse/unanticipated events or patients requesting early trial removal. Events causing serious injury would be unexpected and will be reported to the IRB. This is a relatively small study and thus there is no planned interval analysis of the data.

- **Data Storage and Confidentiality.** The research data will be stored in a database that is password protected in the NYU network drive. The patient data will entered into a coded database for the purposes analysis. Dominique Malacarne and Benjamin Brucker will have access to the decoding key for the purposes of collecting the follow up questionnaires and entering this data into the database.

- **RISK/BENEFIT ASSESSMENT**
  - **Risk.** The additional risk assumed by the subjects due to participating in the PTNS/Sham trial stems from the fact that they will potentially be randomized to the inactive sham treatment arm. The risks of PTNS in general are described above and again are uncommon (1-2%). The sham arm will hold similar yet likely even less common risks, as there will still be an initial needle prick using the sham needle but no puncture of the skin and needle will be retracted into the sham needle sheath. The possibility and nature of risk is thoroughly explained in the consent form that they are given prior to agreeing to study participation.

  - **Protection against Risks.** In an effort to reduce risk and discomfort to the patient, the study needle, grounding pad and energy source will all be placed and controlled by an attending or fellow from the Female Pelvic Medicine and Reconstructive Surgery division of the Urology department. Additionally, questionnaires are as short as possible and a physician from the urology department will be available to answer questions at all times for the patient during their 12 sessions should the device or needle cause them discomfort or should they have any concern. Should patients desire to terminate the PTNS trial at any time, someone from the urology department will be made available to them to remove the needle and disconnect the device. The criteria for

termination of the trial will be patient inability to sustain treatment sessions or patient request to be removed.

- **Potential Benefits to the Subjects.** There are potential individual benefits to the subjects participating in this trial. The possible benefit would be improvement in bladder pain symptoms. This potential benefit could be greater in the PTNS versus sham group, however patients are aware of this prior to consenting to the study.

- **SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT/ASSENT**
  - **Method of subject Identification and Recruitment.** Subjects presenting to NYU Urology Associates, Female Pelvic Medicine and Reconstructive Surgery (FPMRS) division, who meet the inclusion criteria, will be recruited to participate in this study during the enrollment period. Drs. Victor Nitti, Nirit Rosenblum, Benjamin Brucker, Scott Smilen Dianne Glass, Daniel Hoffman and Dominique Malacarne comprise the FPMRS division. Subjects will be identified by the treating physician and the treating physician will introduce the study and request permission for another member of the study team to approach the patient. In order to reduce undue influence over the patients, the primary treating physician will not recruit the subject to participate in the study. Recruiting will be performed either by a Fellow or another attending of Female Pelvic Medicine and Reconstructive Surgery division. Subjects will be assured that participation is completely voluntary and declining will not influence their care.

  - **Process of Consent**. Consent to participate in the study will be performed by one of the physicians in the Female Pelvic Medicine and Reconstructive Surgery division. They are, Dominque Malacarne, Dianne Glass, Daniel Hoffman, Kimberly Ferrante, Victor Nitti, Nirit Rosenblum, Benjamin Brucker, or Scott Smilen. Prior to the consent process a physical exam will need to be performed if there is not one documented from the last three months. At time of the consent process, the PTNS device and characteristics of the treatment sessions will be described to the subjects. It will be made clear to them that the PTNS trial is for research purposes and is not a part of their routine treatment algorithm. The physicians obtaining consent are well trained in the use of PTNS for FDA approved treatment of overactive bladder and will be able to answer general questions about PTNS that the subject may have. The additional time commitment of filling out surveys at baseline, each visit and at the 13th week will be discussed as well

as the commitment to possible randomization to inactive sham treatment arm.

The majority of this patient population are English speaking. Should the subject require a translator, this will be noted on the consent and a signature of the translator will be obtained.

- **Subject Capacity.** Subjects without the capacity to consent for themselves will not be recruited to participate in this study. Any PTNS treatment trial requires that a patient be able to maintain appointments for treatment sessions accurately report on her symptoms associated with BPS/IC.

- **Subject Comprehension.** The PTNS/Sham trial is fairly straightforward. The most difficult thing to describe to patients is the idea of being randomized to PTNS treatment or sham arms for the purpose of assessing PTNS as a viable treatment option for BPS/IC. A physician well trained in symptoms of BPS/IC and the characteristics of PTNS treatment sessions as well as understanding of the PTNS device will be obtaining consent and will be present at the time of treatment sessions. At any point during this process the subject can decline to continue to participate.

- **Debriefing Procedures.** The treatment arm to which each subject is randomized will be withheld from the subject and thus debriefing will be required. This will be done at the end of the 12 week period after the patient has completed all questionnaires. The patient will be allowed to ask any questions and will be given ample time to do so. This session will be with one of the aforementioned physicians.

- **Documentation of Consent.** Consent will be documented with the signature of the subject on a consent form. This form will be stored in the locked office of Benjamin Brucker.

- **Cost to the Subject.** There will be no costs incurred by the subject as a result of the study. All materials for the PTNS/Sham trial will be provided to the patient and will be paid for with Female Pelvic Medicine and Reconstructive Surgery research funds.

- **Payment for Participation.** Subjects will not be paid for their participation in this study.

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