TITLE:

Percutaneous Tibial Nerve Stimulation (PTNS) therapy for female patients suffering from Multiple Sclerosis

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Study Protocol and Statistical Analysis Plan

TITLE

Percutaneous Tibial Nerve Stimulation (PTNS) therapy for female patients suffering from Multiple Sclerosis

INVESTIGATORS

PI: Priya Padmanabhan, MD
Co-investigators: Daniel Menkes, MD Brandon Trivax, DO, Kenneth Peters, MD, Jason Gilleran, MD, Bernadette Zwaans, PhD

I. Background and Rationale

Multiple Sclerosis (MS) is a chronic, progressive inflammatory disorder of the central nervous system. It is caused by loss of myelin, the outer protective layer of the neuron, resulting in a disruption of the signal potentials that flow through the neurons. This can lead to a variety of sensory, visual, and motor disturbances. Demyelinated lesions eventually affect the myelinated nerve tracts that mediate lower urinary tract dysfunction. MS affects almost 1 million people in the United States with the prevalence being two to three times higher in women than in men.[1] Over 80% of MS patients suffer from lower urinary tract symptoms, with bladder overactivity (OAB) and urinary incontinence (UI) being the predominant bladder dysfunctions.[2] OAB is characterized by sudden feeling of urgency, frequent urination, and urge incontinence. Bladder conditions such as OAB have a negative impact on health-related quality of life, and OAB patients have more anxiety and depression than controls. In addition, MS patients with bladder dysfunction are at higher risk for future institutionalization, thus treatments are needed to improve bladder function.[3] MS patients often utilize behavioral and fluid modifications and medications, with a subset progressing to minimally invasive overactive bladder third line therapies, including chemodenervation of the bladder with onabotulinumtoxinA (BTX), PTNS and sacral neuromodulation (SNM). Patient satisfaction and symptomatic improvement are high with all three therapies. Subtle patient characteristics and expectations make one treatment a "better choice" than another. Botox is the only FDA approved treatment, specifically studied to treat neurogenic urgency/ UUI. Percutaneous Tibial Nerve Stimulation (PTNS) is delivered by a slim needle that is placed in the ankle where the tibial nerve is located. When the tibial nerve is stimulated, impulses travel to the nerve roots in the spine to block abnormal signals from the bladder. We propose that the same mechanism that is effective for patients with OAB with be effective in the MS population that also suffers from OAB. PTNS is an FDA approved treatment for OAB and is recommended as third line treatment for OAB by the American Urological Association (AUA) and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU).[4] However, it is not approved for MS and as such these treatments are not covered by insurance. The overall objective success (defined as >50% decrease in urge or urge urinary incontinence (UUI) and 25% reduction in daytime and/or nighttime frequency) of PTNS for OAB has been published and ranges from 60% to 71%.[5-8] The use of PTNS in the neuromodulation of MS-related OAB has only been explored in small case studies, but has demonstrated safety and efficacy.[9] This has limited its inclusion in expert panel consensus recommendations and has prevented FDA approval for the use of PTNS in MS patients with OAB.

Here we propose a pilot, single blind, randomized, sham-controlled trial to assess the benefit of PTNS in treating OAB symptoms in MS patients. The data generated by this study would

provide support for a future multi-institutional, randomized prospective trial. This would be essential for PTNS to gain FDA approval for its use in MS patients, increasing options for durable and cost-effective treatment of neurogenic urinary dysfunction.

II. Objectives and/or Endpoints

The objective of this pilot study is to determine if PTNS therapy improves OAB symptoms in MS patients. We hypothesize that PTNS will significantly improve OAB symptoms in MS patients. We aim at using both subjective and objective measures to measure change in symptom severity (e.g. decrease in urinary frequency, urgency and incontinence).

The **primary outcome measure** will be assessed using the PGI-I, a self-reported measure of symptom improvement after treatment completion. This is a validated 1-question tool to which patients score their urinary tract condition now as compared to how it was before starting treatment. The score ranges from 1-7, with 1 being very much better and 7 being very much worse.[10-12] The **secondary outcome measures** will determine change in urinary symptoms including frequency, urgency, and urinary incontinence, using a 3-day voiding diary, and measure quality of life parameters based on OAB symptoms, using the OAB quality of life short form questionnaire (OABq-SF). All questionnaires are grade A survey tools standardly used for the subjective and objective assessment of OAB symptom and symptom bother. PGI-I questionnaire will be completed at end of 4, 8 and 12 treatments, as well as at follow-up visit (Visit 13), as it is a score of self-reported symptom improvement. Secondary outcome measures will be assessed at baseline (prior to visit 1) and at the end of treatment (visit 13). Unlike idiopathic OAB, OAB symptoms in MS do vary typically in relationship to the disease process, thus closer intervals of assessing change are necessary.

Primary (or general) objectives: Assess the impact of PTNS therapy in female MS patients on subject-reported symptom improvement using the Patient Global Impression of Improvement (PGI-I) score.

Secondary (or specific) objectives: Determine the subjective and objective change in OAB symptoms in response to PTNS therapy using the OABq-SF and 3-day voiding diary.

II. Methodology

This is a pilot, single blind, sham-controlled randomized trial. Female MS patients will be recruited by Dr. Menkes of the Neurology department and by Dr. Brandon Trivax of the PM&R department, as well as private Urology offices. They will be screened by the research nurse coordinator according to the specific inclusion and exclusion criteria.

We anticipate enrolling 34 patients, in this randomized trial, 17 in each study arm. Eligible participants will be consented and randomized into 1 of 2 groups. Patients will be enrolled in the study and randomized:

- After all screening activities have occurred and it has been determined that the patient meets all inclusion criteria without the presence of exclusionary criteria.

- After the patient agrees to enroll and comply with the study protocol, regardless of study group assignment.

Patients will be randomized 1:1 to active PTNS treatment or Sham treatment.

The process of randomization will be as follows:

Randomization will be performed using a table of random numbers. Randomization envelopes will be provided by the study's biostatistician. Randomization assignment will be to either active PTNS treatment or Sham treatment. The randomization envelopes will be securely stored in a locked cabinet. The Research Coordinator(s) will ultimately be responsible for maintaining the confidentiality and security of the randomization envelopes. The biostatistician will prepare more envelopes, if necessary. After the participant is randomized, staff will complete the ***Subject Enrollment and Randomization Log***. The log may be stored in the locked cabinet with the envelopes. Ultimately the log will be stored in the regulatory binder.

All patients who enroll will be seen and treated at the Beaumont Urology clinical research suite.

A. Study Intervention:

PTNS treatment:

Patients will be placed in a comfortable position, sitting or supine. The treatment leg will be propped up comfortably on a footrest but draped and out of view from the patient. A 34-gauge needle electrode will be inserted at a 60-degree angle 5 cm cephalad to the medial malleolus and slightly posterior to the tibia (**Fig. 1A**). A PTNS surface electrode will be placed on the ipsilateral calcaneus as well as 2 inactive sham surface electrodes, 1 under the little toe and 1 on the top of the foot. When the PTNS lead set is connected to the Urgent PC stimulator, a current level of 0.5 to 9 mA at 20 Hz is selected based on each patient's foot and plantar motor and sensory responses. Treatment lasts 30 minutes and given once weekly for 12 consecutive weeks.

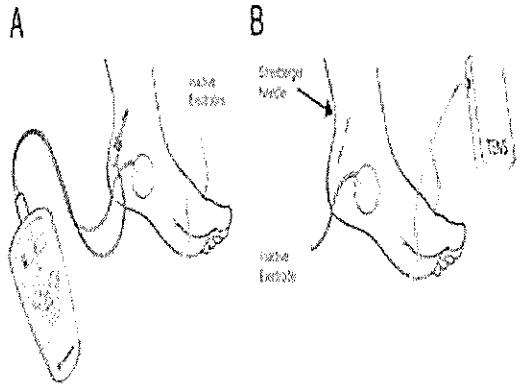

Figure 1: (A) PTNS and (B) Sham Treatment Configurations

Sham treatment:

Sham treatment has been previously optimized by our group.[13] Since patients in the active arm will feel foot stimulation, the sham arm will mimic this feeling without the tibial nerve being stimulated. These patients will be positioned similarly as PTNS patients. The medial aspect of the lower extremity will be palpated and the tibial nerve site will be identified approximately 5 cm cephalad from the medial malleolus. A Streitberger needle will be used at the tibial nerve insertion site to simulate needle placement (**Fig. 1B**). Without puncturing the skin and secured in place with tape. The needle is not connected to any active electrodes, and will not provide any conductive transcutaneous nerve stimulation. Three electrodes will be placed on the patient's foot, two active TENS electrodes and one inactive TENS electrode. The TENS "grounding pad" will be a gel electrode pad from a TENS unit device that is 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. These two electrodes will be connected to the TENS unit lead wires for sham stimulation. A third, inactive, gel electrode, will be placed near the medial aspect of the calcaneus to mimic the PTNS treatment. All TENS electrodes are reusable and may be designated for individual patients. The TENS electrode will be connected by lead wires to the Biostim M7 TENS (Biomedical Life Systems, Vista CA) unit or equivalent set at 20 HZ. The TENS unit will be turned on and stimulation slowly increased to the patient's first sensory level and then turned off.

Open-Label:
At visit 13, after completion of all research related activities, patients will be unblinded to treatment. Patients who were assigned to the sham arm, will be given the option to complete active PTNS therapy and receive open label treatment. If agreed, visit 13 outcome measures will subsequently be used as baseline measures to assess the effect of PTNS therapy on treatment.

B. Study visits:

Screening and Consent Visit 0: Week 0

Eligible patients that have provided voluntary written consent, will complete the enrollment questionnaires including (demographics, medical history, concomitant medications etc.) and OAB-q-SF. If a subject needs to be discontinued from antimuscarinics/beta-3 agonists, this will be discussed after consent. The subject will discontinue the use after the time of consent for $\geq$ 2 weeks and remain off throughout study participation. Patient will need to be screened after washout period to assess if patient still meets eligibility criteria. A urinalysis via urine dipstick and pregnancy test (for women of child-bearing potential) will be performed at screening. *If the urinalysis is positive for leukocytes a urine culture will be sent. Patients with a positive urine culture may be treated per standard of care by the study physician. After treatment is completed, a repeat urine will be checked. If repeat urinalysis is negative, the subject will be allowed to complete the 3-day voiding diary and study activities.* A 3-day voiding diary and instruction will be reviewed with and dispensed to the subject to return at their next scheduled visit.

Subsequent visits that require a urinalysis and are positive for leukocytes if the patient is symptomatic, a culture will be sent per the investigator's discretion.

Enrollment and Treatment 1: Visit 1: (within 3 weeks of visit 0 ± 3 days)
The diary will be collected and reviewed at the first scheduled treatment visit. The RN will verify the subject has remained off antimuscarinics/beta-3 agonists for at least 2 weeks and if eligibility criteria are still met (if applicable). Medication may be resumed in the event participant does not meet study eligibility criteria. After all screening activities have occurred and it has been determined that the patient meets all inclusion criteria without the presence of exclusionary criteria patients will be randomized 1:1 to active PTNS treatment or Sham treatment. A urinalysis via urine dipstick and pregnancy test (for women of child-bearing potential) will be performed. Treatment 1 will be completed at this visit. Patients will be considered enrolled in the study after randomization.

Treatment Visits: 2 - 12: (1 week ± 3 days from last visit)

PTNS and Sham treatments visits will be completed once a week for 12 weeks per study intervention previously described. Each treatment is 30 minutes. A pregnancy test (for women of child-bearing potential) will be performed. Adverse events and concomitant medications will be assessed at each treatment whether sham or active PTNS. PGI-I questionnaire will be completed at end of 4, 8 and 12
treatments, as it is a score of self-reported symptom improvement. After treatment 12 a 3-day voiding diary will be dispensed with instructions for completion to be completed prior to visit 13.

One week post treatment follow-Up visit: Visit 13: (1 week ± 3 days from treatment 12)
One-week post-final weekly treatments (± 3 days), participants will return for an office visit. PGI-I, OABq-SF, and 3-day voiding diary will be collected, and a urinalysis completed. We will also assess for adverse events and concomitant medications at this visit. After all study activities are complete, patients will be un-blinded. Those who were in the sham arm will be offered the opportunity to crossover to the open label treatment phase of the study. Subjects in the open label phase will be offered the same scheduled treatments and follow up as those in the initial active PTNS treatment group. They will have up to 7 days to decide and begin treatment if they would like to continue to the open label treatment phase. Open label treatment 1 may also begin the same day as visit 13 if the patient chooses. Medication may be resumed after study completion.

C. Table of Events
See Figure 2.

D. Subject Discontinuation or Withdrawal
Subjects are free to discontinue study participation at any time upon request. Subjects who discontinue study treatment or active participation in the study will no longer receive PTNS active or sham treatment. When a subject withdraws from the study, the reasons, for withdrawal shall be recorded. Every effort will be made to obtain all end-of-treatment measures.

Additionally, subjects may be withdrawn from the study by the Principal Investigator (PI) for any of the following reasons:

- Subject cannot tolerate study treatment (active PTNS or sham)
- Development of any condition or AE that are clinically significant and may pose additional risk to the participant.
- The PI decides it is in the best interest of the subject to withdraw from the study.
- Subject is unable to follow the Investigators' instructions and/or comply with the study protocol.

TALBLE 1. SCHEDULE OF EVENTS

	Consent and Screening	Enrollment and Tx 1	Tx 2	Tx 3	Tx 4	Tx 5	Tx 6	Tx 7	Tx 8	Tx 9	Tx 10	Tx 11	Tx 12	Follow up	Part 2 Tx1	Part 2 Tx2	Part 2 Tx 3	Part 2 Tx4	Part 2 Tx 5	Part 2 Tx 6	Part 2 Tx7	Part 2 Tx8	Part 2 Tx 9	Part 2 Tx10	Part 2 Tx 11	Part 2 Tx12	Follow up
Visit Window		Within 21days of screening +/- 3 days	Weekly +/- 3 days											7+/-3 days after last Tx	Within 7 days of follow up visit	Weekly +/- 3 days											7+/-3 days after last Tx
Visit	Visit 0	Visit 1	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18	V 19	V 20	V 21	V 22	V 23	V 24	V 25	V 26
Consent	X																										
Eligibility	X																										
Demographics, medical history	X																										
OABq-SF	X													X													X
PGI-I					X				X				X	X				X				X				X	X
3-day Voiding Diary returned		X												X													X
Pregnancy test[a]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X												X													X
PTNS/SHAM treatment[c]		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Un-Blinding														X													

a. A urine pregnancy test will be completed for those of childbearing potential.
b. Urine culture required if urinalysis is positive for Leukocytes at screening, positive cultures will be treated by the study physicians per standard of care. Subsequent visits that require a urinalysis and are positive for leukocytes if the patient is symptomatic, a culture will be sent per the investigator's discretion.
c. All PTNS or sham sessions will be completed by an experienced Urology Research Nurse (treatments will be completed weekly +/- 3 days for 12 consecutive weeks)

E. Replacements

Subjects who have been randomly assigned to receive treatment and who subsequently discontinue prematurely from the study may be replaced by another subject. The ultimate goal is to have 34 patients complete the study, 17 in each arm. If/when a subject withdraws from the study prior to completing study at visit 13, an additional subject will be enrolled. Each subject will be assigned their own unique study identification number.

Subjects who fail to satisfy inclusion and exclusion criteria at screening may be rescreened at the discretion of the PI.

IV. Risks and Benefits

PTNS or Sham Treatment

Less frequent (occurring from 1% to 10% of the time):

- Discomfort/pain/pressure/tingling at, or near, the stimulation site, or the subject's lower leg or foot
- Redness/inflammation at, or near, the stimulation site
- Possible worsening of OAB symptoms (Stimulating the nerves can either improve, worsen, or have no effect on symptoms) i.e. increased frequency, urgency, nocturia/ leaking due to the procedure

Rare (occurring less than 1% of the time):

- Skin irritation
- Electrode burn
- Allergic reaction to adhesive pad gel
- Numbness of toes
- Allergic Reaction
- Possible increase in lower extremity pain or pelvic pain

If a patient is required to discontinue antimuscarinics/beta-3 agonists with a "washout" period to participate in the study there is a chance they may return to baseline urinary symptoms.This may include but is not limited to an increase in urinary frequency, urgency, and urinary leakage.

Possible Risk of Breach of Privacy and Confidentiality

There is a rare risk of breach of privacy and data confidentiality (release of information which personally identifies the subject). Confidentiality procedures will be strictly adhered to when transferring, managing, and analyzing study data. The subject will be assigned a unique study identification number and research information will be stored in a locked, secure cabinet in the Urology Research suite with access limited to authorized research personnel. Study data will be maintained in a password protected file on a shared network that can only be accessed by Urology research personnel.

Possible Benefits

- Improvement of bladder symptoms
- Improvement in quality of life

V. Eligibility Criteria

Inclusion criteria:

- Women with diagnosis for Multiple Sclerosis (CIS, RRMS, SPMS, and/or PPMS), 18 years of age or older
- A score of $\geq$ 4 on question 1 of the OAB-q symptom bother short form completed by patient at screening
- Average urinary frequency of $\geq$ 8 voids per day as recorded on initial 3-day voiding diary
- Self-reported bladder symptoms > 3 months
- Discontinued antimuscarinics/beta-3 agonists for $\geq$ 2 weeks and remain off throughout study participation.
- Capable of giving informed consent
- Ambulatory and able to use toilet independently without difficulty
- Capable and willing to follow all study-related procedures
- If of childbearing age, agree to practice approved birth-control methods (oral contraceptives, condom barrier, injection, diaphragm or cervical cap, vaginal contraceptive ring, IUD, implantable contraceptive, surgical sterilization (bilateral tubal ligation), vasectomized partner(s))
- Subject agrees not to start any new treatments for urinary symptoms (medication or otherwise) during the treatment and follow-up periods.
- Subject agrees to maintain a stable dose on all current medications throughout the treatment and follow-up period.

Exclusion criteria:

- Pregnant or planning to become pregnant during study duration
- BTX use in bladder or pelvic floor muscles within past 6 months
- Pacemakers or implantable defibrillators
- Current urinary tract infection
- Active use of neuromodulation in any other form.
- Current use of Transcutaneous Electrical Nerve Stimulation (TENS) in pelvic region, back or legs
- Previous PTNS treatment
- Participation in any clinical investigation involving or impacting gynecologic, urinary, or renal function within past 4 weeks

VI. Data Analysis Plan

The primary outcome measure is the PGI-I score. The PGI-I will determine the patient perception of symptom improvement based on a single question. The PGI-I score given by the patient will range from 1-7, with 1 being very much better and 7 being very much worse. Scores

of 1 and 2 will be considered as clinically meaningful improvement in OAB symptoms. The percent of patients with significant symptom improvement will be compared between the active and sham treatment groups using a one-WAY ANOVA test.

The secondary outcome measures include the 3-day voiding diary and the OABq-SF questionnaire. For both, baseline measures will be taken prior to first treatment and again at the completion of treatment. The change in OAB symptoms (e.g. number of daytime voids and urgency episodes) and the change in OAB symptom bother (e.g. how have your symptoms adjusted planned activities?) between baseline and at the end of treatment will be calculated for each study participants. The average change in symptom (bother) will subsequently be compared between active and sham treatment groups using two-WAY ANOVA.

Finally, patient assigned to receive sham treatment have the option to crossover into active treatment after completion of the sham portion. For patients who complete both sham and crossover studies, data from OABq-SF and 3-day voiding diary will be analyzed using a one-WAY ANOVA in which the average values of three time points (baseline, end of sham treatment, end of crossover) are compared.

As this study is a pilot study, no official power analysis was performed. The sample size was chosen based on the limitations of the budget, which was largely driven by the cost of the PTNS and sham needles. A total of 34 patients will be enrolled in the study, 17 per treatment group. The 17 patients that are randomized into the sham treatment have the option of completing the active treatment (crossover). Data (OABqSF, 3-day voiding diary, PGI-I) will continue to be collected during the crossover study and analyzed as described above.

VII. Data and Safety Monitoring Plan

Ongoing safety monitoring will be performed by the study staff, including the Principal Investigator (PI) and co-investigators. The PI will have ultimate responsibility of assuring patient safety. Safety issues will also be addressed in the annual reports to Beaumont's Investigational Review Board (IRB).

Additional data safety monitoring procedures include:

- Research Administration's Clinical Research Quality and Process Improvement Program (CRQIP) will perform in-house monitoring of the first patient enrolled after the completion of visit 1
- An audit of the study records after the first 10 patients are enrolled and at the half way point of enrollment by an RN in the Urology Research Department that is not directly involved with the research study. This will be done to ensure the safety of subjects and lack of significant adverse effects.

As an on-going plan, any adverse effects occurring during the treatment phase and determined to be related, potentially related, possibly related, or probable to the study treatment (prolonged irritation, hemodynamic changes, significant pain, or other deemed significant by clinicians) will be reported to the research nurse and then to the PI at the time of the event. Adverse events,

serious adverse events, and unanticipated problems not listed in the risks section of this protocol will be reported per IRB guidelines.

Subject records will be reviewed to verify case report form (CRF) completion and delinquencies, and capture protocol deviations and frequency of unanticipated problems/adverse events. To identify, evaluate, and prevent adverse events, the total number of events will be reviewed, as well as the details of each event, including visit number and severity. Data will be reviewed to identify trends and possible concerns. Enrollment data will direct recruitment efforts and assist in study planning.

The overall objectives of routine monitoring are to:

- Document clinical study progress.
- Document that the protocol and associated forms are current.
- Obtain and review current clinical data, reports, and source documents.
- Review the overall study status including verification of the study files. All required documents and records should be accurate, complete, and current.
- Confirm that all subjects have signed the informed consent form.
- Confirm that all enrolled subjects have met the eligibility criteria.
- Verify accuracy of transferring data from source document(s) to the CRFs to the database.
- Confirm complete, accurate, and timely event reporting.
- Confirm adequacy of staff and facilities.
- Review communication records.
- Verify identification and reporting of protocol violations.

Outcomes of all scheduled and unscheduled study monitoring will be documented. Follow-up action items will be included in the report. The monitoring summary report will be forwarded to the PI and research coordinator.

Quality Control and Quality Assurance (QC/QA)

The PI or designee has primary responsibility for QC/QA activities of the data. Beaumont's Research Institute also audits investigator-initiated studies to ensure compliance with consent processes and reporting requirements. The key QC/QA activities for the study will be:

- Clearly formatted and carefully constructed CRF;
- Sign-Off Procedures for all CRFs;
- Verification of subject eligibility at each visit

A database will be created utilizing RedCap, MS Excel, or equivalent software. Only designated study personnel will have access to the database, which will be stored on the Urology Research Department's shared drive. Access to the computerized system will be password protected. To ensure accuracy of data entry, database entries will be cross-checked against source documents. The shared drive is backed up nightly to ensure minimal data loss, even in the most catastrophic system failure. The database will be active until all study visits are completed, final monitoring activities have been conducted, and all data queries have been resolved. After that time, the database will be locked, prohibiting any changes to the data.

All study records, including both paper and electronic, will be stored in accordance with all federal and institutional requirements, including, but not limited to, the HIPAA Privacy Rule, the Food and Drug Act, and Medicare policy. The stored data will be kept in a secure, protected manner. All records will be retained, at a minimum, for eleven years beyond study completion.

VIII. Adverse events and serious adverse events

- AEs will be collected and reported from the start of study treatment, visit 1 until completion of the participant's last study-related procedure, which may include final follow-up. SAEs related to study procedures will be collected from the time of participant began study treatment, at visit 1 through the final follow-up contact is completed.
- PIs are not obligated to actively seek new onset AEs or SAEs after the protocol-defined reporting period; however, if the PI learns of any SAE and he/she considers the event to be reasonably related to the study intervention or study participation, the PI must promptly notify the IRB.
- The PI will assess the severity and causality of AEs and SAEs and classify the event as Related, Probably Related, Possibly Related, Probable, or Not-related to the Study.
- The PI will provide follow-up of each AE/SAE until resolution, the condition stabilizes, the event is otherwise explained, or the participant is lost to follow-up. The PI will report all AEs and SAEs to the IRB of record, according to policy. SAEs will be reported within 24 hours of knowledge of the event.

Unanticipated Problems (UP), include any incident, experience, or outcome which <u>meets all three</u> of the following criteria:

- **Unexpected (in terms of nature, severity or frequency) given the known risks associated with the study treatment. Please refer to Section IV.**
- **Related or possibly related to participation in the research.**
- **Suggests the research places participants at a greater risk of harm than was previously known or recognized.**

Unanticipated Problems will be reported per IRB policy.

VIV. Summarize Existing Study Data

The use of PTNS in the neuromodulation of MS-related OAB has only been explored in small case studies but has demonstrated safety and efficacy. PTNS and SNM seem to be effective and safe therapeutic options for treating lower urinary tract symptoms in MS patients principally in case of overactive bladder (OAB) symptoms. Given their safety and efficacy, stimulations such as PTNS could be considered as a first-line treatment for OAB in MS patients, also considering that they are often preferred by patients to other commonly used treatments.[9] Long-term sustained therapeutic effects of PTNS in MS patients were shown in a study with 21 patients (5 men and 16 women) with MS and PTNS treatment. In this study, a year of PTNS treatment with a tapering protocol of 6, 9 and 12 months of therapy was applied. A total of 21 patients were enrolled in the study. The results showed a significant improvement in frequency, urgency, nocturia, urge incontinence and voided volume at 6, 9, and 12 months when compared to baseline.[14] Pacini et al, investigated using PTNS in MS patients with neurogenic overactive

bladder. Patients were evaluated using voiding diaries and questionnaires after receiving 12, 30-minute sessions of PTNS, performed twice a week. 21/29 subjects were considered responders, with a reduction ≥50% of urgency episodes.[15] The limitation on this study was it did not include a sham group. Additional contemporary clinical outcome data is needed. The data generated by this study would provide support for a future multi-institutional, randomized prospective trial. This would be essential for PTNS to gain FDA approval for its use in MS patients, increasing options for durable and cost-effective treatment of neurogenic urinary dysfunction.

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