

## Clinical feasibility study, implantable tibial nerve stimulator (ITNS)

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## 1 Introduction

*Study title:* Clinical feasibility study, implantable tibial nerve stimulator (ITNS); ITNS-01.

*Study sponsor:* Nine Continents Medical, Inc., 302 Alden Lane, Livermore, CA 94550 USA.

*Study objectives:* To report feasibility data for safety and effectiveness of the study device.

*Study device:* Nine Continents Medical implantable tibial nerve stimulator (ITNS) model 9C-680 with programmer model 9C-580.

*Intended use:* The study device is intended for treatment of the symptoms of overactive bladder (OAB), including urinary urge incontinence and significant symptoms of urgency-frequency alone or in combination, in patients who have failed or could not tolerate more conservative treatments.

## 2 Study design

*Type of design:* Single-arm longitudinal design with no implanted comparator.

*Study sites:* Single site, in the United States.

*Number of subjects:* The investigator will implant a study device in each of 10 subjects, to permit gathering meaningful data for evaluating study endpoints while constraining the number of subjects exposed to residual risks. This sample size conforms to FDA recommendations (FDA, 2013-10-01).

*Study duration:* One year total, comprising six months for enrolling and implanting 10 subjects, and 26 weeks for follow-up. The follow-up period allows for biological stabilization at the implant site and for assessing the effect of neuromodulation therapy on OAB symptoms.

*To minimize or avoid bias:* This protocol specifies inclusion and exclusion criteria and standardized methods and timing for assessing variables. It requires standardized case report forms for recording variables, and it specifies methods for analyzing variables.

### 2.1 Inclusion and exclusion criteria

The target population is the population indicated for third-line therapy for OAB. To avoid exposing subjects to risks in the absence of any anticipated benefit, exclusion criteria are intended to prevent implantation in subjects for whom success is unlikely due to general health issues. Any exclusion criterion disqualifies a subject from further participation in the study.

Although this is a feasibility study, it uses the same inclusion and exclusion criteria planned for a pivotal study. The purpose is to gain experience evaluating potential subjects with these criteria and to select a study population representative of the intended target population.

<i>Type of criteria</i>	<i>List of criteria</i>
Inclusion criteria	Age 18 years or older
assessed at pre-screening evaluation.	Documented diagnosis of overactive bladder
Each subject must	Documented failed behavioral intervention and/or physical therapy
meet all.	Documented failed first drug for overactive bladder
	Documented failed second drug for overactive bladder

<i>Type of criteria</i>	<i>List of criteria</i>
Inclusion criteria assessed at screening visit. Each subject must meet all.	Life expectancy of at least one year Capable of tolerating the implantation procedure Ambulatory and able to use the toilet independently and without difficulty Able to sense and tolerate posterior tibial nerve stimulation (transcutaneous test)
Inclusion criteria based on 3-day pre-therapy diary. Each subject must meet at least one.	Average daily voids during waking hours $\geq 11$ Average daily voids interrupting sleep $\geq 2.0$ Average daily voids associated with urgency $\geq 4$ Average daily incontinence episodes $\geq 1$
Exclusion criteria assessed at pre-screening evaluation, and confirmed by interview at screening visit. No subject may meet any.	Predominant stress incontinence For females, pelvic organ prolapse with POP-Q $\geq$ grade II Neurologic disease, e.g. MS, Parkinson's Abnormal upper urinary tract function Neurogenic bladder Bladder stone or tumor BMI $> 40$ Chronic pelvic pain Urinary fistula Peripheral neuropathy History of failed neuromodulation for overactive bladder Uncontrolled bleeding disorder End stage renal failure, GFR $< 35$ , or dialysis Untreated diabetes or A1C $> 7$ Implanted pacemaker, defibrillator, or neurostimulator History of pelvic cancer within the past two years Condition requiring magnetic resonance imaging (MRI) Condition requiring diathermy Metallic implant in planned site of study device For females, pregnant For females, planning to become pregnant For females, given birth in the last 6 months For females, of child-bearing potential and not willing to practice a medically-approved method of birth control during the study

<i>Type of criteria</i>	<i>List of criteria</i>
Exclusion criteria assessed at physical examination and tests at screening visit. No subject may meet any.	Anatomical restriction preventing device placement Skin lesions or compromised skin at the implant site For females, pelvic organ prolapse with POP-Q $\geq$ grade II Post-void residual > 150 cc Urinary tract mechanical obstruction due to urethral stricture Urinary tract mechanical obstruction due to bladder neck contracture In males, urinary tract mechanical obstruction due to BPH Vesicoureteral reflux Cystoscopic abnormalities that could be malignant Current cystitis Current urethritis Gross hematuria In females, positive pregnancy test
Exclusion criteria assessed at pre-screening evaluation, screening visit, and pre-implantation evaluation.	Any other medical condition with potential effect on bladder function, as assessed by investigator Any other medical condition that could compromise the safety of the subject, as assessed by investigator

## 2.2 Medicare beneficiaries

Medicare beneficiaries with symptoms of overactive bladder could benefit from the device if it performs as intended. Prevalence of overactive bladder is approximately 30 % in the general population 65 to 74 years old (Stewart, et al., 2003). Therefore a significant percentage of the population eligible for Medicare due to age has symptoms of overactive bladder. The percentage of the population eligible for Medicare due to disability, who also have symptoms of overactive bladder, is not known. Criteria in §2.1 exclude individuals eligible for Medicare due to ESRD but do not exclude those eligible due to ALS.

## 2.3 Endpoints

A clinical feasibility study is a clinical investigation that is commonly used to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan an appropriate pivotal study (FDA, 2013-10-01). A feasibility study does not collect definitive evidence; consequently it does not require statistical hypotheses or classifying objectives and endpoints as primary or secondary.

Section 5 on page 15 provides rationales for endpoints.

<i>Type of endpoints</i>	<i>List of endpoints</i>
Safety	Incidence, severity, and relatedness of all adverse events and device deficiencies.  Stability of neuromodulation pulse amplitude required to evoke paresthesia or muscle response (“threshold”).

<i>Type of endpoints</i>	<i>List of endpoints</i>
Effectiveness, OAB symptoms Averages per 24 hours, measured with 3-day voiding diaries	Incontinence: Improvement = 50 % reduction from baseline of number of episodes. Dryness = 0 episodes. Frequency: Improvement = 50 % reduction from baseline of voids during waking hours exceeding 7. Cure = number of voids during waking hours $\leq 7$ (note: FDA uses the term “cure” to describe normal frequency). Nocturia: Improvement = 50% reduction from baseline of number of voids interrupting sleep. Urgency: Improvement = 50% reduction from baseline of number of voids self-reported with moderate to severe urgency.
Effectiveness, responder criterion	Subject demonstrating 50 % reduction in at least one relevant OAB symptom above and no worsening of their relevant symptoms overall. Here “relevant” means meeting the inclusion criterion for a symptom at baseline, and “overall” means average of percentage changes over all relevant symptoms.
Effectiveness, quality of life	OAB-q, short form symptom bother (Coyne, Matza, & Thompson, 2005). GRA, global response assessment (Proper, et al., 2006).

### 3 Methods for assessing and recording variables

#### 3.1 Procedures

The study will include procedures listed below and will document results with standardized case report forms (CRFs). Refer to designated forms for detailed instructions for each procedure, and refer to §3.4 for procedure timing requirements.

<i>Procedure</i>	<i>Form #</i>	<i>Purpose</i>
Pre-screening evaluation	D-00288	Preliminary assessment of medical records for inclusion and exclusion criteria for potential subject.
Informed consent	R-00108	Documentation of potential subject’s informed consent, required for enrollment in the study and participation in procedures required specifically for the study.
Screening visit	D-00290	Record of demographics. Confirmation of inclusion and exclusion criteria through subject interview; physical examination; urodynamics, cystoscopy, urinalysis, and pregnancy tests (subjects without documented urodynamics and cystoscopy results prior to screening will be required to undergo these tests before completion of the screening visit).

<i>Procedure</i>	<i>Form #</i>	<i>Purpose</i>
Pre-therapy diary	D-00291	3-day voiding diary to assess baseline incontinence, frequency, nocturia, and urgency. OAB-q SF for quality of life (QOL). Subjects may optionally continue the diary for up to 7 days total. Subjects who cannot or will not complete a diary will exit the study.
Pre-implantation evaluation	D-00292	Assessment of routine blood chemistry, and OAB symptom severity from pre-therapy diary, to qualify or disqualify subject for device implantation.
Implantation procedure	D-00293	Implantation of ITNS per IFU. Threshold assessment with external device and ITNS. ITNS therapy programmed off for a 4-week healing period.
4-week follow-up visit	D-00294	Threshold assessment with ITNS for changes since implantation. ITNS programmed to threshold amplitude and daily therapy (for potentially reducing time to therapy effect).
6-week follow-up visit	D-00295	Threshold assessment with ITNS for changes after two weeks of daily ITNS therapy. ITNS programmed to threshold amplitude and weekly therapy (to preserve device longevity).
Daily therapy diary (optional)	D-00296	3-day voiding diary to assess changes from baseline OAB symptoms after 2 weeks of daily ITNS therapy. OAB-q and GRA to assess QOL changes. Subjects may optionally continue the diary for up to 7 days total.
19-week follow-up visit	D-00297	Threshold assessment with ITNS for changes after 13 weeks of weekly ITNS therapy. ITNS programmed to threshold amplitude and weekly therapy.
Weekly therapy diary	D-00298	3-day voiding diary to assess changes from baseline OAB symptoms after 13 weeks of weekly ITNS therapy. OAB-q and GRA to assess QOL changes. Subjects may optionally complete a second weekly therapy diary at 26 weeks after implantation. Subjects may optionally continue each diary for up to 7 days total.
26-week follow-up visit	D-00299	Final safety assessment 26 weeks after implantation. Non-responders (as assessed with the latest weekly therapy diary) require device explantation; responders continue with site's standard of care.
Explantation procedure	D-00300	Explantation of ITNS for any subject with an unplanned exit during the study or for a non-responder after 26 weeks of implantation.
Adverse event	D-00301	Assessment of nature, onset, actions taken, outcome, relatedness, and seriousness for any unfavorable medical occurrence, including patient complaints.

<i>Procedure</i>	<i>Form #</i>	<i>Purpose</i>
Device deficiency	D-00302	Record of nature, onset, and actions taken for any device malfunction, use error, or inadequate labeling.
Unplanned exit	D-00303	Record of any exit from the study due to withdrawal of consent, death, or loss to follow-up (including date and type of three attempts to contact the subject). Withdrawal of consent for dissatisfaction with device or procedure also requires an adverse event form.
Protocol deviation	D-00304	Description of type and reason for any protocol deviation, where a required item was not performed, performed early or late, or performed not according to protocol.

### **3.2 Study devices and equipment**

*Summary description:* The study device is a miniaturized implantable pulse generator with an integrated electrode lead. The pulse generator is powered by a primary (non-rechargeable) lithium cell. It can be programmed non-invasively by timed applications of an external magnet, or it can be programmed and interrogated non-invasively by external programmer model 9C-580.

*Device manufacturer:* Nine Continents Medical, Inc., 302 Alden Lane, Livermore, CA 94550 USA.

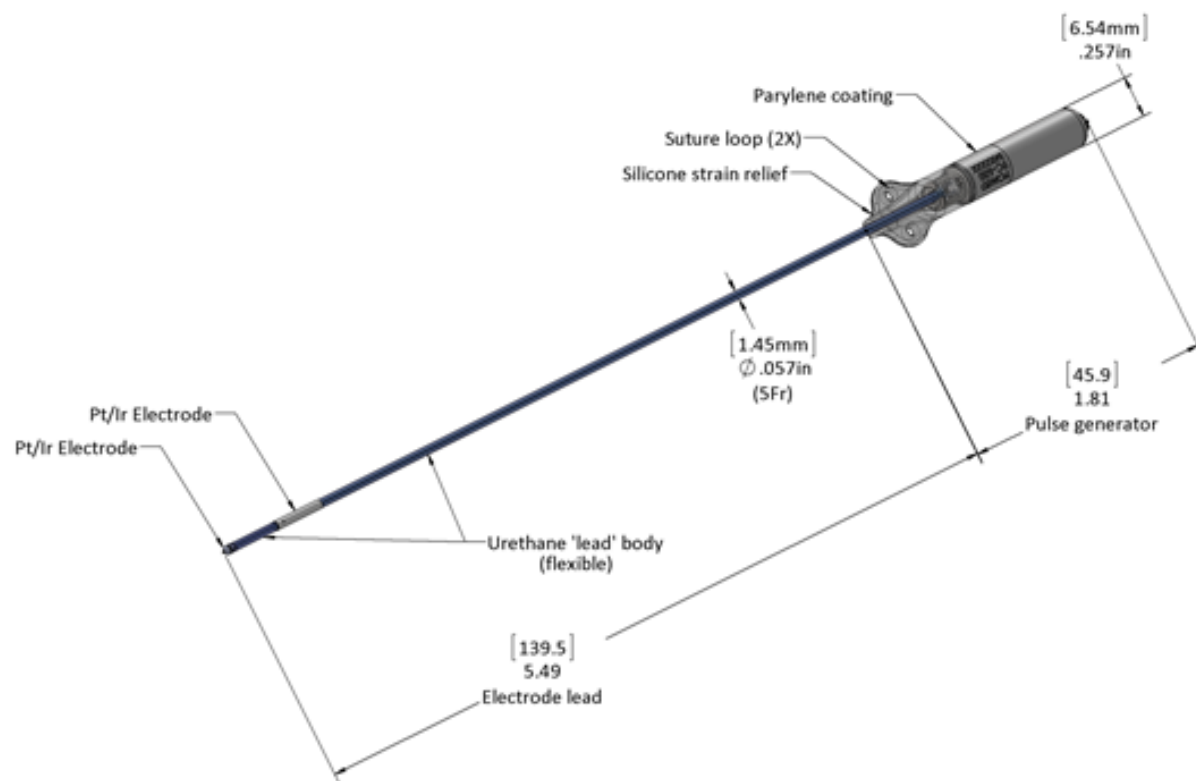
*Device identification:* Model number 9C-680.

*Device traceability:* Each device has a unique serial number.

*Device purpose:* The pulse generator automatically provides stimulation at a pulse pattern and frequency preset to match those of percutaneous tibial nerve stimulation (PTNS), without requiring clinic visits for the patient to receive therapy.



*Materials in contact with tissues or body fluids:* Refer to the drawing below. The study device does not contain medicinal products, human or animal tissues or their derivatives, or other biologically active substances.



*Training and experience needed to use the device:* This is a prescription device for implantation by a physician. The investigator will complete study and device training before using the device.

*Medical or surgical procedures involved:* The miniaturized pulse generator is permanently implanted via a percutaneous procedure. The implant site is subcutaneous in the medial lower calf, distal to the gastrocnemius muscle. The electrode-lead integrated with the pulse generator is advanced distally from the same incision with a marketed implant kit. The study device provides electrical pulses to the posterior tibial nerve at a point approximately 5 centimeters proximal to the medial malleolus, which is the same location where PTNS is applied.

*Background for study:* Refer to sponsor's report of prior investigations R-00105 for a detailed list of verification and validation studies successfully completed for ITNS model 9C-680 and programmer model 9C-580. Briefly, ITNS validation studies included sterile packaging, sterilization, biocompatibility, and a six-month animal study with eight ITNS implanted in four sheep. ITNS verification studies included electromagnetic compatibility; electrical specifications, safety, and reliability; mechanical specifications, safety, and reliability; and device longevity and lithium cell integrity. Programmer verification studies included electromagnetic compatibility and electrical safety. ITNS and programmer software were validated. Risk analysis included system-level functions, RF wireless technology, and cybersecurity.

### 3.3 Subjects

*Point of enrollment:* The investigator will enroll study subjects at approved investigational sites after completing an investigator's agreement and receiving notification from the sponsor that the study has started.

*Concomitant medication:* Medication to be used during the study is at the investigator's discretion, however any change in medication with urinary effects or side effects after the screening visit must be recorded as a protocol deviation.

*Replacement of subjects:* This study has inclusion and exclusion criteria (§2.1 on page 3) intended to ensure that subjects complete the protocol after they receive the study device. Consequently this protocol has no provision for replacement of subjects after implantation.

*Efforts to minimize missed visits and drop-outs:* The sponsor or sponsor's designee will monitor the investigation as described in its established monitoring procedure and will promptly inform the investigator concerning missing data or missed visits. The investigator will remind subjects of scheduled visits by telephone or by E mail, and will document at least three (3) efforts to contact subjects who miss a visit (e.g. via registered mail, E mail, or telephone). If a patient cannot be contacted, this becomes a withdrawal or discontinuation.

*Incentives for subjects:* The investigator may provide special incentives to subjects for study compliance, but the compensation may not be so large as to unduly encourage the subjects to participate.

*Withdrawal or discontinuation:* A subject may withdraw from the study at any time, for any reason, and without stating a reason. Withdrawal or discontinuation will not prejudice a subject's future medical care by the investigation team or investigation site. Upon withdrawal or discontinuation a subject will have their ITNS explanted. An investigator may discontinue a subject's participation for any of the reasons below:

- Any unanticipated adverse device effect (see adverse event CRF) which is, in the opinion of the investigator, related to the treatment and will endanger the well-being of the patient if treatment is continued;
- Development of any concurrent illness, infection, or condition that might interfere with the investigation;
- Non-compliance with the clinical investigation procedures deemed by the investigator to be sufficient to cause discontinuation; or
- Any other problem deemed by the investigator to be sufficient to cause discontinuation.

*Follow-up care:* Subjects who do not qualify as responders at the 26-week visit will have their ITNS explanted. The investigator will provide medical care for the subjects after the clinical investigation has been completed, conforming to their standard practice.

### **3.4 Procedure timing requirements**

**Informed consent** must be signed before a subject undergoes any test or procedure not required for routine care outside the study. For example, the following tests may be performed before signed informed consent, provided they are necessary for a patient's routine care: blood and urine analyses, physical examination, urodynamics, cystoscopy, and pre-therapy diary. The study device must never be used without prior signed informed consent. The investigator or an individual they designate must meet with each prospective subject to explain the study and alternatives before requesting consent.

The **pre-therapy diary** provides a baseline for calculating symptom improvement after implantation of the study device, consequently any improvement of OAB symptoms in the pre-therapy diary due to prior therapy and medications could mask the effectiveness of the study device. Investigational sites may use the study's pre-therapy diary form for routine care outside the study. However, any pre-therapy diary used for the study must start:

1. At least 4 weeks after the most recent:
  - Use of any anti-muscarinics, beta-3 adrenergic agonists, or other OAB medications;
  - Dose change of any other medications with urinary side effects (e.g. Flomax, tri-cyclic antidepressants, diuretics); or
  - TENS use (back, pelvic, or legs).
2. After sufficient time for symptoms to return to baseline levels of after stopping PTNS or Botox for OAB. This time varies from subject to subject.

When completing the **pre-screening**, **screening**, and **pre-implantation** case report forms, the investigator may use results from tests performed for a patient's routine care outside the study, provided that the results are documented in the patient's medical record, and remain valid for the subject's current medical condition in the investigator's medical judgment. For example, this may include results from blood and urine analyses, physical examination, urodynamics, cystoscopy, and a pre-therapy diary as described above. Prior measurements of PTNS current required for motor response or sensation may be used.

The table below provides additional procedure timing requirements:

<i>From</i>	<i>To</i>	<i>Min weeks</i>	<i>Max weeks</i>
Pre-screening evaluation	Screening visit	0	4
Informed consent	Screening visit	0	4
Screening visit	Pre-implantation evaluation	0	7
Pre-implantation evaluation	Implantation procedure	0	4
Implantation procedure	4-week follow-up visit	3	5
4-week follow-up visit	6-week follow-up visit	2	3
6-week follow-up visit	Daily therapy diary (optional)	0	2
6-week follow-up visit	19-week follow-up visit	12	14
19-week follow-up visit	Weekly therapy diary	0	2
Implantation procedure	26-week follow-up visit	25	27
26-week follow-up visit	Explantation (if non-responder)	0	4
Unplanned exit	Explantation (if implanted)	0	4

### 3.5 Adverse events and device deficiency definitions

The investigator will record and classify all adverse events and device deficiencies. They will record the onset and resolution times of each adverse event, noting the method of resolution.

The investigator will record all adverse events and classify them as:

- Device-related, procedure-related, or non-related.
- Serious or non-serious.
- Unanticipated adverse device effects or other.

An *adverse event* is any unfavorable medical occurrence, unintended disease or injury, or unfavorable clinical signs (including abnormal laboratory findings), in a subject, whether device-related, procedure-related, or non-related. It is also any such event, in a user or other person, if related to the study device.

A *device-related* adverse event is caused or contributed to by the study device. This definition includes adverse events involving insufficient or inadequate instructions for the study device, malfunction of the study device, or use error or intentional misuse of the study device.

A *procedure-related* adverse event is caused or contributed to by a procedure required to use the study device.

Because of the difficulty of determining the root cause of genitourinary events, the investigator will categorize events conservatively as either device- or procedure-related unless there is clear evidence of other causation.

A *serious* adverse event is one that either:

- a) Led to death, or
- b) Led to serious deterioration in the health of the subject, that either resulted in:
  - 1) A life-threatening illness or injury, or
  - 2) A permanent impairment of a body structure or a body function, or
  - 3) In-patient or prolonged hospitalization, or
  - 4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

Planned hospitalization for a pre-existing condition, or a procedure required by the investigational plan, without serious deterioration in health, is not considered a serious adverse event.

An *unanticipated adverse device effect* (UADE) is a serious adverse event that is device- or procedure-related, and is not identified in the protocol by its nature, incidence, severity, or outcome. The table below identifies potential serious adverse device effects:

<i>Nature</i>	<i>Incidence</i>	<i>Severity</i>	<i>Outcome</i>
Implant-procedure related complication: infection; damage to nerves, tissues, or vessels; migration; erosion or extrusion; pain at implant site.	< 40%, based on initial clinical experience of SNS	Serious	Surgical revision including explant; intent-to-treat failure.
Increase in the pulse amplitude required for neuromodulation, beyond the range of the pulse generator.	< 15 % (one event maximum in an early feasibility trial)	Serious	Surgical revision and/or loss of significant device function.
Study device malfunction causing or contributing to failure to deliver neuromodulation therapy.	< 15 % (one event maximum in an early feasibility trial)	Serious	Surgical revision and/or loss of significant device function.

Initial clinical experience of SNS: SNS studies reported frequent adverse events, including pain at the stimulator site (3.3 to 19.8% of patients), pain at the lead site (4.5 to 19.1% of patients), lead migration (2.2 to 8.6% of patients), infection/irritation (2.2 to 14.30% of patients), electric shock (5.5 to 10.2 7.9% of patients) and need for surgical revision (6.25 to 39.5% of patients). In most studies, the need for surgical revision occurred in greater than 30% of patients (Gormley, et al., 2014).

The investigator will report all device deficiencies involving the study device, whether or not they involve adverse events. A *device deficiency* is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. This includes malfunctions, use errors, and inadequate labeling.

*Timing:* The investigator will report serious adverse events to the sponsor and IRB within 24 hours. They will report other adverse events and device deficiencies to the sponsor within 30 days.

### **3.6 Activities performed by sponsor**

The investigator will perform or supervise all required study procedures. The sponsor's personnel may assist at study device implant, assessment of adverse events and device deficiencies, and measurement of response threshold.

### **3.7 Investigator selection and training**

The sponsor will select a study site and investigator capable of recruiting sufficient numbers of eligible subjects, representative of the target population for the study device.

To help ensure the safe, proper, and consistent use of the investigational device, the sponsor will conduct a training program to educate investigators and their staff on the use of the study device. This training will consist of didactic instruction, covering the device functions and principles of operation. Additionally, the training will highlight the important or unique aspects of the clinical study, such as screening, obtaining informed consent, the follow-up schedule, data collection methods, and adverse event reporting. Finally, the training will include a cadaver study.

## **4 Data management**

### **4.1 Case report forms (CRFs)**

Refer to §3.1 on page 6.

### **4.2 Procedures used for data review, database cleaning, and issuing and resolving data queries**

The sponsor will enter all CRF data into a central database. The sponsor will review all incoming data to identify inconsistent or missing data as well as any adverse events. The sponsor will promptly address any data issues with the investigator.

### **4.3 Procedures for verification, validation and securing of electronic clinical data systems, if applicable.**

This clinical investigation will use paper CRFs rather than an electronic clinical data system.

### **4.4 Procedures for data retention and specified retention period**

The sponsor and investigator will maintain the clinical investigation documents for a minimal period of five (5) years after the clinical investigation is completed, or longer depending on national requirements. They will take measures to prevent accidental or premature destruction of these documents and ensure these are filed in a secure place. Investigator or sponsor may transfer custody of records to another person or party and document the transfer at the investigation site, or at the sponsor's facility.

The investigator will maintain all source documents required by the protocol, including laboratory results, supporting medical records, and signed informed consent forms.

### **4.5 Other aspects of clinical quality assurance, as appropriate**

The measures described in §4.1 through §4.4 provide appropriate clinical quality assurance for an early feasibility study.

#### 4.6 Study report

The sponsor will provide a study report with tables listed below. Each table will provides data organized by subject unless otherwise noted.

<i>Table</i>	<i>Information provided</i>
Study summary	Investigational plan title and version; IDE number and approval date; clinical investigation suspension and/or completion dates.
Sites	Site number, name, and address; investigator names; IRB name and approval date; number of subjects consented and number of subjects implanted at the site.
Subject demographics	Age, sex, race, and ethnicity. (NIH recommends collecting race and ethnicity).
Subject accountability	Date completed for each procedure required by the protocol, with total number of subjects that complete each procedure (CONSORT diagram data).
Medications	Type, dose, and dose interval for any medications with urinary effects or side effects.
Procedure timing	Compliance with protocol requirements for minimum and maximum time between procedures.
Unplanned exits	Any exits for withdrawal of consent, death, or loss to follow-up.
Protocol deviations	Type of deviation, reason for deviation, description of deviation, and effect of deviation (management of potential adverse effects on rights, safety, or welfare of subject and/or scientific soundness of the study).
Adverse events	Dates of onset and resolution, seriousness, relatedness, and description of adverse event.
Device deficiencies	Date of onset, type and description of device deficiency.
Thresholds	Lowest amplitudes at which paresthesia or motor response occurred, at screening visit; implantation; and 4-, 6-, 19-, and 26-week follow-up visits.
Durations	Time from implantation procedure start to end, and time from implantation procedure end to discharge.
Pre-therapy diary	Average events per 24 hours: incontinence, frequency, nocturia, and urgency. Whether or not subject met each of the 4 inclusion criteria.
First therapy diary	Average events per 24 hours: incontinence, frequency, nocturia, and urgency. Improvement or worsening from baseline after 2 weeks of daily therapy.



<i>Table</i>	<i>Information provided</i>
Second therapy diary	Average events per 24 hours: incontinence, frequency, nocturia, and urgency. Improvement or worsening from baseline after 13 weeks of weekly therapy.
Quality of life	From pre-therapy, first therapy, and second therapy diaries: OAB-q Part A and Part B scores and GRA scores, with changes from baseline.
Device accountability	For each ITNS released for investigational use: delivery site and date; implant attempt subject #, date, and outcome; explantation reason and date; return reason and date; and returned product analysis result and date.

The report will include descriptive statistics (average and standard deviation) for all effectiveness endpoints, and will employ graphical displays such as spaghetti plots to represent individual changes.

## **5 Rationales for endpoints**

*Safety endpoints:* The adverse event endpoint in this study comes from FDA guidance (FDA, 2011-03-08) and is often used in medical-device studies. The neuromodulation pulse amplitude endpoint comes from the sponsor and is intended to detect functional changes in the interface between the stimulation electrode and the biological substrate it stimulates, analogous to pacing thresholds measured in studies of cardiac electrode-leads.

*Effectiveness endpoints:* OAB is a symptom complex with four factors: incontinence, frequency, nocturia, and urgency. For incontinence, objective endpoints for improvement and cure come from FDA guidance (FDA, 2011-03-08). For the other OAB factors, objective endpoints for improvement are similarly defined as a 50 % reduction in pathological episodes: frequency (voids during waking hours exceeding 7), nocturia (voids awakening from sleep), and urgency (voids with moderate to severe urgency). Subjective endpoints (quality of life) are a questionnaire selected for OAB symptoms including urinary incontinence and a global response assessment (Peters, et al., 2010).

### **5.1 Rationale for the criterion for improvement in frequency**

Frequency improvement is defined as a 50 % reduction from baseline of the number of voids during waking hours exceeding 7. This criterion takes into account that traditionally up to 7 micturition episodes during waking hours has been considered normal (Fitzgerald & Brubaker, 2003). This criterion is analogous to the criteria for improvement for the other three OAB components (incontinence, nocturia, and urgency), all of which require a 50 % improvement in the number of pathological events. Seven or fewer daytime voids are not pathological. A 50 % improvement in daytime voids exceeding 7 is a 50 % improvement in pathological events. This same endpoint (50 % improvement in frequency exceeding normal) is currently used in an IDE trial for another OAB device, NCT02873312 on clinicaltrials.gov.

### **5.2 Rationale for the criterion for worsening**

*Background:*

- In pre-IDE Q161967 the sponsor proposed defining a responder as a subject with significant improvement of at least one OAB symptom (e.g. 50 % better). FDA provided feedback: “Patients would be considered ‘responders’ if they improve significantly by one of those criteria but are overall worse in terms of their overactive bladder (OAB) symptoms. Criteria

for ‘responder’ should depend upon the underlying diagnosis/diagnoses and require that the patient meet the elements for all relevant diagnosis.” The sponsor was concerned that this required a subject to demonstrate significant improvement for every relevant symptom to qualify as a responder, even though improvement in a single symptom could have clinical significance.

- Therefore in Q161967/S001 the sponsor proposed defining a responder as a subject with significant improvement of at least one symptom and no significant worsening of any other symptom (e.g. 50 % worse). FDA provided feedback again: “Worsening of incontinence episodes and the number of voids would be any increase over the respective baseline number. A threshold of a 50% increase in order to be counted as worsening is arbitrary and lacks clinical meaning.” The sponsor was concerned that with this definition, a vanishingly small worsening of one symptom could classify a subject as a non-responder, despite a significant improvement of one or more other symptoms.

To address FDA’s and sponsor’s concerns, this protocol defines a responder as a subject demonstrating significant improvement of at least one relevant OAB symptom (e.g. 50 % better), and no worsening of their relevant symptoms overall (worsening would be any increase overall). Here “relevant” means meeting the inclusion criterion for a symptom at baseline, and “overall” means average of changes over all relevant symptoms.

For example, a subject with a baseline diary showing daily averages of 9 voids during waking hours, 3 interrupting sleep, 5 with urgency, and 0.3 with incontinence would meet the study’s inclusion criteria in §2.1 for nocturia and urgency (i.e. the subject would have two relevant symptoms). If their therapy diary showed daily averages of 1 void interrupting sleep and 6 with urgency, that would correspond to a -67 % change (improvement) in nocturia but a +20 % change (worsening) in urgency, or an overall change of -44% (improvement). That subject would qualify as a responder.

### **5.3 Dichotomous and continuous criteria**

This study requires a dichotomous “responder” criterion for an individual subject, to inform a decision about allowing the subject to keep the study device after the 26-week follow-up visit. As discussed above, FDA guidance also recommends dichotomous “improvement” criteria for individual subjects, e.g. 50 % symptom improvement.

As a feasibility study, this protocol does not establish prospective criteria for effectiveness for all subjects as a group. A pivotal study would establish hypothesis testing for statistics such as percentages of subjects meeting a dichotomous criterion, and averages over subjects of a continuous parameter. To inform the design of the pivotal study, this feasibility study will report descriptive statistics (including average, median, minimum, maximum, and standard deviation) for all effectiveness endpoints, and will employ graphical displays such as spaghetti plots to represent individual changes.

### **5.4 Effectiveness data from prior studies**

Many prior studies of PTNS have presented mean or median improvements, or responder percentages for subjective endpoints, but only a limited number have provided responder percentages for objective endpoints. The available studies show positive responses to PTNS, which are perhaps comparable to responses to SNS, although inclusion criteria and responder definitions varied across studies:



- In a study of subjects with urge incontinence, 18 were treated with 12 PTNS sessions, and 17 were treated with stimulation sessions in the medial part of the gastrocnemius muscle as controls (Finazzi-Agro, et al., 2010). A responder was defined as a subject showing > 50 % reduction in urge incontinence episodes. There were 71 % responders in the PTNS group and 0 % in the control group ( $p < 0.001$ ).
- In a study of subjects with OAB (defined as clinical complaints of urinary frequency, nocturia, and/or urgency incontinence), 8 were treated for 12 weeks with PTNS (Souto, Reis, Palma, Palma, & Denardi, 2013). The percentage with urinary incontinence (any involuntary leakage of urine) decreased from 94 % to 11 %. The percentage with nocturia (waking one or more times at night to void) also decreased from 94 % to 11 %.
- In a study of subjects with OAB (defined as > 7 voids or > 2 urge incontinence episodes per 24 hours) who had previously demonstrated a reduction of more than 50 % in incontinence episodes or voids with PTNS, 8 had their PTNS treatment stopped for at least 3 months and then were treated for 12 months with an implanted PTNS device (van der Pal, van Balken, Heesakkers, F.M.J., & Bemelmans, 2006). Defining a responder as a subject with > 50 % improvement in an endpoint and no increase in the other two endpoints, the table below shows percentages of responders (from 24-hour voiding diaries):

<i>Responders</i>	<i>Baseline to month 3</i>	<i>Baseline to month 6</i>	<i>Baseline to month 12</i>
Voids	13%	25%	25%
Nocturia	38%	50%	25%
Incontinence	88%	63%	50%

- In a study of subjects with OAB (defined as > 8 voids per 24 h, or > 3 urge urinary incontinence episodes per week, or nocturia; and phasic detrusor contractions in the filling phase of saline cystometry), 43 were treated for 6 weeks with PTNS (Yoong, Ridout, Damodaram, & Dadswell, 2010). A positive response was defined as: (i) OAB symptoms no longer being bothersome; (ii) reduction by half in frequency episodes and (iii) reduction by 25% in IIQ-7 outcomes. A positive response rate of 69.7 % was found. Yoong, et al., did not specify whether “frequency episodes” meant episodes per 24 hours or episodes exceeding 8 per 24 hours.

SNS studies showed comparable results (Medtronic, Inc., 2011):

- For subjects with urge incontinence, 61 % of those undergoing SNS test procedures (naïve to SNS) experienced > 50 % improvement in leaking episodes. Of those who went on to a permanent implant, 75 % remained improved at six months.
- For subjects with urgency-frequency, 36 % of those undergoing SNS test procedures experienced > 50 % improvement in urgency-frequency parameters (decrease in voids/day or increase in volume/void). Of those who went on to a permanent implant, 34 % remained improved with a > 50 % decrease in voids/day, and 54 % remained improved with > 50 % increase in volume/void.

## **6 Rationale for type of design**

This clinical feasibility study has a single-arm longitudinal design with no implanted comparator. The study’s small sample size, selected to limit exposure to unforeseen risks during this first human use of the study device, does not provide sufficient power to test effectiveness changes versus a concurrent control group.

This feasibility study has effectiveness endpoints for two other reasons: (a) to gain experience with the effectiveness assessments planned for a pivotal study; and (b) to assess an individual subject's symptom improvement with device use, to inform a decision about continued use after 26 weeks.

## **7 Future pivotal study**

If there is a successful completion of this clinical feasibility study, the sponsor will propose a pivotal study to demonstrate safety and effectiveness for regulatory approval. If the feasibility study proceeds as planned, the pivotal study will be based on the same procedures and endpoints, together with the additional information gained about effectively conducting a study in the target population.

## **8 Deviations from clinical protocol**

*Prior approval:* The investigator will obtain prior written approval of a request for deviation from the protocol, from the investigator's IRB, if the deviation affects subject's rights, safety, and well-being, or the scientific integrity of the clinical investigation.

*Emergency:* Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the IRB. Such deviations shall be documented and reported to the sponsor and the IRB as soon as possible.

*Records:* The investigator will use the protocol deviation CRF listed in §3.1 on page 6 for recording and reporting protocol deviations to the sponsor, and to the IRB or EC if required above.

*Corrective and preventive actions:* The sponsor will review all reported deviations, and will cooperate with the investigator to implement corrective and preventive actions where appropriate. If necessary the sponsor may take additional action including terminating the investigator's participation in the investigation.

## **9 Suspension or premature termination of the clinical investigation**

*Criteria:* In response to a concern about the rights, safety, or well-being of subjects, or about the scientific soundness of the study, which cannot be resolved by other means:

- An investigator may suspend or prematurely terminate the study at his or her investigational site, after consultation with the sponsor.
- The sponsor may suspend or prematurely terminate the study at one, several, or all investigational sites, after consultation with the investigator(s) concerned.

*Follow-up:* During suspension the investigator will continue scheduled follow-up, provided this does not adversely affect the rights, safety, or well-being of subjects. After premature or scheduled termination of the clinical study, the investigator will provide medical care for the subjects after the clinical investigation has been completed, conforming to their standard practice.

## **10 Amendments**

The sponsor and investigator will record approval and justification for any amendment to an approved protocol. If changes affect the scientific soundness of the clinical investigation, or affect the health, welfare, safety and rights of patients, the investigator and/or sponsor will obtain

written approval by the investigator's institutional review board (IRB) and FDA before implementing changes. If changes are merely administrative in nature, the investigator will notify their site's IRB.

## **11 Device accountability**

The sponsor will ship or convey investigational devices only to a qualified investigators participating in this clinical investigation. The sponsor will not ship or convey investigational devices to any site until evidence of IRB approval has been provided to the sponsor or sponsor's designee.

Investigators will control access to investigational devices, and will only use investigational devices in the clinical investigation and according to the protocol.

The sponsor will keep records to document the physical location of each investigational device. Record(s) will include information documenting devices shipped or conveyed, devices at investigation sites, devices disposed of, and devices returned.

The investigator will keep records documenting the receipt, use, return and disposal of the investigational devices, which will include:

- Date of receipt,
- Identification of each investigational device (serial number or unique code),
- Use-before date, if applicable,
- Date or dates of use,
- Subject identification,
- Date on which the investigational device was returned, or explanted from subject, if applicable, and
- Date of return of unused, expired or malfunctioning investigational devices, if applicable.

## **12 Statements of compliance**

The investigator will conduct the clinical investigation in accordance with this protocol and an investigator agreement executed before beginning the study.

The sponsor will provide clinical investigation insurance for subjects. This will continue to cover direct costs associated with any device deficiencies after the subject exits from the study.

The clinical investigation will be conducted in compliance with Title 21 of the Code of Federal Regulations ("21 CFR"), Parts:

- 50, Protection of Human Subjects.
- 54, Financial Disclosure by Clinical Investigators.
- 56, Institutional Review Boards.
- 812, Investigational Device Exemptions.

## **13 Publication policy**

For this clinical feasibility study, the investigator agrees to maintain confidentiality and refrain from publication without the sponsor's prior written approval.