TITLE:

The Effect Of Acute Pudendal Nerve Stimulation On Leak Point Pressure In Women Urodynamic Early Feasibility Study

NCT05128682

Approval date: 04/05/2022

Study Protocol and Statistical Analysis Plan

The Effect Of Acute Pudendal Nerve Stimulation On Leak Point Pressure In Women Urodynamic Early Feasibility Study

Investigator Initiated Protocol Number: CLN-0212

Sponsor: Kenneth Peters, MD

Version Date: 03/25/2022

CONFIDENTIAL

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1 Revision Control & Approvals

1.1 Revision Control

Revision	Date	Update Description	Author/Owner
01	12-DEC-2021	Initial Release	
02	25-MAR-2022	Revisions to Eligibility Criteria	

2 Investigator

Role	Contact Information
Principle Investigator	Kenneth Peters, MD

3 Protocol Synopsis

Title:	The effect of acute pudendal nerve stimulation on leak point pressure in women urodynamic early feasibility study
Protocol Number:	CLN-0212
Study Design:	An early feasibility prospective single-arm study
Purpose:	Evaluate the changes in stress introduced Urethral Leak Point Pressures (ULPP) and other urodynamic measurements in response to acute pudendal nerve stimulation (PNS) in patients with a pre-existing implanted urological neurostimulator (Medtronic InterStim™) stimulating the pudendal nerve. Ultimately these data may support the development of subsequent studies of a sensor-controlled neuromodulation treatment for Stress Urinary Incontinence (SUI) and or Mixed urinary Incontinence (MUI).
Objectives:	Primary Objectives: 1. Gain initial insights on the effect of acute PNS 2. Gain initial insights on the changes in LPP upon acute PNS. Secondary Objectives: 1. Gain initial insights on the effect of acute PNS on the urethral pressure profile (UPP) and other urodynamic measurements.
Endpoints:	Primary Endpoint: 1. Identification of all study-related adverse events 2. Measurement of the changes in ULPP with acute PNS compared to without stimulation. Secondary Endpoints:

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	1. Measurement of UPP and other urodynamic measurements with and without programmed pudendal nerve stimulation.
Study Description:	A urodynamic test (UDT) for eligible subjects with and without acute PNS will be conducted. Prior to introducing the acute PNS, the subject's original stimulation properties will be turned off. The implanted neurostimulator device will be programmed to deliver acute PNS per individual tolerance level with the objective of increasing external urethral sphincter pressure. The ULPP during Valsalva maneuver or forceful coughing will be assessed with and without acute PNS. The ULPP will be assessed at increasing bladder volumes until major detrusor instability, significant leakage (more than drops, stream) or subject discomfort (strong desire to void) is observed. Finally, a UPP with PNS set in an on/off cycling regimen will be conducted to observe the effect on pressures along the length of the urethra.
Visit Schedule:	There are 3 study visits: 1) enrollment (remote visit), 2) acute stimulation/UDT (in person) visit, and 3) a follow up phone call. The second visit is expected to last about 90 minutes
Study Duration:	Approximately 6 months from the first enrollment until completion of data collection.
Study Population:	Female patients with an implantable PNS device.
Number of subjects:	Up to 15 subjects
Inclusion Criteria:	The subject must meet all the following inclusion criteria: 1. Women between the ages of 18 and 85 years old, inclusive. 2. Implanted with a neurostimulation device for at least 3 months prior to consent (Medtronic InterStim neurostimulator models 3023, 3058, 97810, or similar;) 3. Implanted with a tined lead that is placed and functionable at the pudendal nerve (Medtronic model 3889 or similar) 4. Is capable of understanding clinical study procedures and giving informed consent. 5. Willing and able to visit the clinic for the UDT evaluation (study procedure) Note: No more than eight subjects having no history of SUI as determined by the investigator.
Exclusion Criteria:	The subject must not meet any of the following exclusion criteria: 1. Medically unstable at time of study and unsafe to undergo urodynamic testing as determined by the investigator 2. Active bladder cancer 3. History of pelvic radiotherapy 4. Active gross hematuria 5. Active symptomatic urinary tract infection (UTI) 6. Active symptomatic uncontrolled bladder instability as determined by the investigator

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	7. History or symptoms of cystocele, enterocele or rectocele of grade 3 or 4. Per the medical record or as determined by the investigator 8. Presence of an artificial urinary sphincter 9. Women who are pregnant and/or have given birth in the previous 12 months 10. Any medical condition (e.g. Multiple Sclerosis, spinal cord injury, mobility) or uncontrolled chronic disease (e.g. diabetes, renal diseases that requires dialysis) that would interfere with the patient's ability to comply with the protocol and/or may affect the outcome of this study or safety of the subject as determined by the investigator 11. BMI>39
Data Collection	**Screening data:** ▪ Demographics ▪ Medical History ▪ Urinary incontinence history ▪ Current Medication ▪ Eligibility ▪ Neurostimulator system (device & electrode) placement and identifiers ▪ Prior UDT chart data (optional) **PNS device settings:** ▪ Device stimulation settings ▪ Patient sensations **PNS procedure data:** ▪ Urodynamic test including ULPP with and without PNS ▪ Electromyography test (if separately) ▪ Urethral Pressure Profile (optional) ▪ Adverse events

4 Study Rational

4.1 Background

Aoki, et al., reported that urinary incontinence symptoms are highly prevalent among women, have a substantial effect on health-related quality of life and are associated with considerable personal and societal expenditure [1]. Two main types are described: stress urinary incontinence (SUI), in which urine leaks in association with physical exertion, and urgency urinary incontinence (UUI), in which urine leaks in association with a sudden compelling desire to void. Women who experience both symptoms are considered as having mixed urinary incontinence (MUI)." Overall, SUI is more common (49%) followed by MUI (29%) and pure urge urinary incontinence (21%) [2]. According to Funk, et al., SUI is a highly prevalent condition affecting approximately 13% of women aged 19-44 years and 22% of women aged 45-64 years.[3,4] These women suffer from unpredictable episodes of urinary leakage, which profoundly impairs their quality of life.[5-7] In addition, the economic costs are substantial, totaling over $20 billion per year in the United States, with 50-75% of these costs due to routine care from incontinence pads, diapers, laundry, dry cleaning, odor control, bed pads and skin care products.[7,8]

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Although there are a number of therapies and treatments for SUI, including conservative measures and minimally invasive options, the efficacy of such therapies is limited and supporting data is lacking.[9-10] There remains a substantially large patient population who have not had success in their treatment or, as with some patients, having undergone implanted meshes and suspension procedures are experiencing significant morbidity.[11] Furthermore, in many individuals, urinary incontinence is complex, involving urge urinary incontinence (UUI), SUI and potentially other related disorders such as Interstitial Cystitis (IC). [12]

Implantable neuromodulation systems have been approved in the US and available to treat the symptoms of UUI and idiopathic urinary retention since the 1990's.[13,14] These systems provide a beneficial treatment for UUI symptoms by delivering electrical stimulation to the nerves of the sacral spine or pudendal nerve in an open loop manner, without being modulated by any feedback from sensed physiologic conditions. Furthermore, these existing systems are not approved to treat SUI since these systems do not deliver a treatment capable of addressing the mechanism of SUI[10,14]. Therefore, these existing systems are not capable of treating SUI or MUI, which constitutes a large percentage of the population (78%) with urinary incontinence. Moreover, individuals with UUI alone that are indicated for sacral nerve stimulation (SNS) may eventually develop SUI, resulting in the SNS systems no longer effectively treating all UI symptoms. [5]

This research may help in the development of a novel on-demand neuromodulation therapy for stress and mixed urinary incontinence. This technology may become a valuable treatment for women that have failed more conservative options.

4.2 Study rationale

The primary purpose of this early feasibility prospective study is to gain initial understandings on the effect of acute PNS on the changes in LPP at different bladder volumes. This study is the starting point to gain evidence that the abdominal pressure increases could be detected quickly enough to control the delivery of stimulation to the pudendal nerve resulting in an external sphincter and pelvic floor contraction, thereby preventing an SUI event.

5 Objectives and Endpoints

The goal of this study is to collect and analyze subject's urodynamic data, including pressure flow variables with and without PNS during induced elevated abdominal pressure episodes.

Ultimately these data are intended to support the development of subsequent studies of a sensor-controlled neuromodulation treatment for stress and mixed urinary incontinence.

5.1 Primary Objectives

1. Gain initial insights on the effect of acute PNS
2. Gain initial insights on the changes in LPP upon acute PNS

5.2 Primary Endpoints

1. Identification of all study-related adverse events
2. Measurement of the changes in LPP with acute PNS compared to without stimulation

5.3 Secondary Objective

1. Gain initial insights on the effect of acute PNS on the urethral pressure profile (UPP) and other urodynamic measurements.

5.4 Secondary Endpoint

1. Measure UPP and other urodynamic measurements with and without programmed pudendal nerve stimulation

6 Methodology

This study is a feasibility, prospective single arm study. Female subjects with a preexisting operating neurostimulator that is stimulating the pudendal nerve are having a standard urodynamic test (UDT) with and without acute PNS.

6.1 Number of subjects

Up to 15 subjects

6.2 Study Duration

Approximately 6 months from the first enrollment until completion of data collection.

6.3 Study follow-up

There are 3 scheduled visits in this study:

1. Screening and Enrollment Visit
   The first visit includes administering informed consent via telephone script and confirming eligibility. Informed Consent (ICF) must be obtained from each eligible patient prior to any study activities. Through the telephone script, potential subjects will consent to receive a copy of the full informed consent form and to provide some information over the phone, listed below:
   - Medical history
   - Urinary incontinence history
   - Neurostimulator information
   - Previous UDT and UPP studies (optional)

   If a subject doesn't meet study eligibility criteria, he/she should not be consented or enrolled to this study.

2. Stimulation Visit
   The second visit includes completion of the full informed consent form and urodynamic testing with and without stimulation. This visit will be conducted within 4 weeks of the Screening and Enrollment Visit. This visit will be conducted in the clinic/site in person. Before any additional study activities occur, the full study consent form must be completed. Prior to beginning the UDT, a urinalysis will be performed to screen for a UTI and a urine pregnancy test will be performed. Before UDT begins, a prophylactic antibiotic will be administered to the patient to prevent urinary tract infection (UTI). In this visit the neuromodulation settings of the implanted device will be adjusted to deliver acute simulation. At the end of the UDT the settings will be

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returned to the previously set therapeutic values. The neuromodulation settings constitute the "dose" and can include the voltage/current amplitude, frequency, pulse width, on time/off time duration and electrode polarity assignments. These parameters are limited by the available ranges of the approved neurostimulation device and will be adjusted during the study by the principal investigator to stay within the safe and comfortable levels for each individual study subject.

3.

The following information will be collected during this visit:

- Stimulation previous and current properties/setting
- Urethral Pressure Profile
- UDT data, including Leak Point Pressure (LPP) with and without stimulation
- Complications

Inspire Medical Systems, Inc. is collaborating with Beaumont on this study. Inspire hopes to use insight gained from this trial to guide the creation of a new implantable neurostimulator for patients with stress and mixed incontinence. We have a data sharing agreement in place with Inspire. They are not the study sponsor. They have provided funding for the study to take place and will receive de-identified results. They may wish to be present at some, or all, of the UDT visits. They may attend in person or remotely, via audio headsets. Their presence at these visits would serve to provide real-time feedback and suggestions to study staff. Participants will have the right to decide whether or not representatives from Inspire may be present at their UDT visit.

The purpose of real-time collaboration between study staff and Inspire is to make decisions about the best time points and/or bladder volumes to stop for leak point pressure testing, and whether leak point pressure testing should be repeated with stimulation off if no leaks are elicited with stimulation off. The representatives from Inspire may provide additional guidance, as needed, for troubleshooting and ensuring no important data collection is missed.

4. Follow-Up Phone Call

The third visit will take place by phone and will include assessment of any adverse events which may develop following the Stimulation Visit. This will take place 1 week (+/- 2 days) after the Stimulation visit.

6.4 End of Study Definition

The end of the study is defined as completion of Visit 3: Follow-Up Phone Call.

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6.5 Table of Events

Activities	Visit 1: Screening and Enrollment *Phone visit*	Visit 2: Stimulation Visit *Within 4 weeks of Visit 1*	Visit 3: Follow-Up Phone Call *1 week +/- 2 days from Visit 2*
Phone Consent	X		
Eligibility	X		
Medical History	X		
Urinary Incontinence History	X		
Neurostimulator Data	X		
Full Informed Consent		X	
Urinalysis		X	
Pregnancy Test[1]		X[1]	
Urodynamic Equipment Setting		X	
Stimulation Setting/Programming		X	
Antibiotic		X	
Urodynamic test with & without acute PNS		X	
UPP (optional)		X	
Adverse Event Assessment		X	X
Study Exit			X
[1]*For women of childbearing potential*			

7 Study Intervention Description

7.1 Study test equipment placement & setting

7.1.1 An oral antibiotic will be administered to the patient prior to UDT to reduce the risk of infection. The patient will receive either nitrofurantoin (100mg) or Bactrim Double Strength (80mg Trimethoprim/400mg sulfamethoxazole). Which antibiotic is prescribed will be based on patient known drug allergies and investigator determination.

7.1.2 Set up the urodynamic machine equipment per site's UDT operation procedure protocol.

7.1.3 Perform setup calibration to confirm proper UDT system function per institution practices. The subject will be asked to perform Valsalva and coughing to establish baseline pressure levels that the physician will intend to achieve during the study.

7.1.4 The neurostimulator's physician programmer will be used to program the implanted pulse generator deliver stimulation to the pudendal nerve via the implanted neurostimulator leads.

Note: For the testing, patient may be placed in a reclined, seated or standing position.

7.2 Acute Pudendal Nerve Stimulation (PNS) Setting

7.2.1 For the acute stimulation setting, the existing settings may be utilized or other settings within the range approved for use. Gradually increase amplitude and record urethral pressure and

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amplitude per investigator.

7.2.2 Continue to increase amplitude progressively until discomfort noted and then reduce incrementally to the last acceptable level to the subject.

7.2.3 Per investigator, the electrode configuration and stimulation parameters may be changed as needed and 7.2.1-7.2.2 repeated.

7.2.4 Turn stimulation off.

7.3 Determine Leak Point Pressure Without and With Stimulation

7.3.1 Move the subject into a sitting or other position as per clinician.

7.3.2 Ensure acute stimulation parameters are set as determined in 7.1.4, above, so that the stimulation pulse train will be delivered continuously when manually turned on. The stimulation will be manually turned off for the infusion delivery periods.

7.3.3 Adjust the urodynamic system to infuse saline at 50 mL, 100mL or increments per investigator at a 50 mL/min infusion rate per physician's discretion.

7.3.4 Start the urodynamic saline infusion into the bladder until the first volume is reached (recommended at either 50mL, 100mL or per investigator) and pause the infusion.

7.3.5 Observe for urinary leakage while patient performs one or more coughs or Valsalva maneuvers with stimulation off to assess LPP.

7.3.6 Turn on stimulation per 7.1.4 and repeat the LPP assessment, using one or more coughs or Valsalva maneuvers as confirmation. Turn off stimulation. Note: This step may be omitted if no leak is observed in 7.3.5 or per physician's discretion.

7.3.7 Continue the urodynamic saline infusion (end the infusion pause mode) and fill the bladder to the next assessment point and stop infusion. Repeat the LPP with stimulation off, and then with stimulation on per 7.3.5above7.3.6.

7.3.8 Continue performing Valsalva and forceful coughs at additional bladder volume intervals without and with stimulation (steps) until patient has strong desire to void, bladder reaches major detrusor instability, patient has significant leakage (more than drops), patient has discomfort or any other reason per PI.

NOTES:

A. The stimulation will be manually turned off while filling the bladder to the subsequent measuring point and for the off-stimulation LPP assessment. Stimulation is turned on only when the LPP assessments with stimulation are conducted.
B. The stimulated periods shall not continue for more than approximately 60 seconds with no less than approximately 60 seconds of rest between stimulation periods.
C. LPP assessment with or without stimulation may be repeated per PI discretion. Stimulation settings may be changed during the LPP assessment or before a repeat assessment.
D. Bladder fill-in (infusion) rate and LPP assessment points (bladder volumes) are per physician discretion, UDT standard operation protocol and subject's UI profile.
E. Infusion of saline to compensate for significant leakage as needed will be completed at PI discretion.

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7.4 Conduct UPP (Urethral Pressure Profile), Optional

Complete prior to filling bladder during UDT, and again when the bladder is filled to the point where the patient expresses a strong urge to urinate.

7.4.1 The subject remains in a reclined, seated position or per investigator.

7.4.2 Connect the UPP catheter to the automatic indexing arm and adjust the traverse rate to 1/3 mm/sec. As an alternative, the UPP catheter may be withdrawn manually without the use of an automatic indexing arm: In this case, the steps of 1.0 cm or as per PI shall be achieved by using a reference mark on the catheter and annotating the urodynamic pressure recording correspondingly.

7.4.3 Ensure that the Pudendal neurostimulator is off.

7.4.4 Begin with the catheter placed such that the pressure sensitive portion is initially just inside the bladder. Complete 3 slow pulls.

7.4.5 Turn on stimulation per 7.2 and repeat the 3 UPP pulls as above

7.4.6 Once having completed the UPP turn off stimulation.

Note: UPP recording may be repeated per physician's discretion

7.5 End of Test

7.5.1 Remove all testing equipment (i.e. catheters, electrode pads)

7.5.2 Record any complication and adverse events

7.5.3 Discharge subject

7.6 Concomitant Therapy

No concomitant therapies are allowed during the urodynamic test procedure.

8 Risk/Benefit Assessment

This is an early feasibility study utilizing commercially released, market approved devices. Both the UDT system (Laborie, Sweden) and the implantable neurostimulator (Medtronic, USA) have been approved by the FDA for their respective indications. The study does not include any invasive nor experimental interventions/treatment. This study is considered low risk since the subjects that will be enrolled already have an implanted pudendal nerve stimulator and have already incurred the risks of the implantation procedure and the initial neurostimulation treatment as detailed in the neurostimulator manual[1,2]. In addition, all the equipment needed for the study such as the urodynamic testing system are FDA regulated and used as standard of clinical testing in urology.

[1]*https://www.medtronic.com/us-en/healthcare-professionals/products/urology/sacral-neuromodulation-systems/interstim-ii/indications-safety-warnings.html*

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8.1 Known Potential Risks

Potential risks and harms are listed below in alphabetical order. These potential risks were identified consistent with Beaumont practices in research using urodynamic testing and electrical stimulation.

8.1.1 Potential Risks Associated with Urodynamic Test

The risks in this category are related to those of Urodynamic Testing. The estimated probability of these risks occurring is Less Frequent (occurring more than 1% but less than 10% of the time):

- Abrasion to rectum from rectal manometry catheter
- Abrasion to urethra from urethral catheter
- Anxiety
- Discomfort or pain during catheter insertion
- Mild cramping
- Minor bleeding
- Skin irritation (skin electrode adhesive)
- Temporary inability to urinate
- Urinary Tract Infection (UTI)

8.1.2 Potential Risks Associated with use of an antibiotic

Less Frequent (occurring more than 1% but less than 10% of the time):

- Diarrhea
- Nausea and vomiting
- Cramping

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

- Headache
- Itching
- Rash
- Allergic reaction

8.1.3 Potential Risks Associated with Acute Pudendal Nerve Stimulation

The harms in this category only include those related to changing the device settings to deliver stimulation in a slightly different way that is still within the allowable ranges of the approved neurostimulator device. The differences in stimulation settings may include greater amplitude, different pulse width, frequency and different electrode configuration. The risks associated with the implanted stimulation system already exist in these patients since they were already implanted for the current indicated PNS treatment and the incremental risk incurred due to participation in the study is only due to the temporarily changed stimulation settings.

The incremental risks a subject may experience during the study procedure due to adjustment of the electrostimulation parameters and the delivery of acute vs. continuous PNS are alphabetically identified below. The estimated probability of these risks occurring is More Frequent (occurring more than 10% of the time):

- Temporary discomfort due to high level of stimulation
- Temporary dysesthesia (abnormal sensation)

- Temporary pain

The incremental risks a subject may experience after the conclusion of the study procedure due to adjustment of the electrostimulation parameters and the delivery of acute vs. continuous PNS are alphabetically identified below. The estimated probability of these risks occurring is Rare (occurring less than 1% of the time):

- Discomfort due to high level of stimulation
- Dysesthesia (abnormal sensation)
- Pain

8.2 Known Potential Benefits

There are no proven major short- or long-term benefits anticipated for the study subjects or society in general. Study subjects may learn more details regarding the nature of their urinary function. From a societal perspective, the data generated from these studies may prove to be essential foundational learning that may support progression toward an effective treatment for stress and mixed urinary incontinence.

8.3 Assessment of Potential Risks and Benefits

The risks to the study subjects result from performing the standard urodynamic test and delivering acute PNS from an already active implantable PNS device. Urodynamic testing is a commonly performed, standard of care, procedure used for assessing urinary incontinence and other voiding disfunctions. Furthermore, the PNS stimulation parameters are within the allowable ranges of the approved stimulation device.

The following activities will be implemented for risk mitigation:

- Only highly experienced health care professional in the field of clinical urology will be selected to perform this study.
- Only subjects meeting the inclusion and exclusion criteria will be enrolled in the study to minimize any pre-disposition to any potential harms.
- The subject's physiologic status will be continuously monitored during the clinically indicated procedure.
- A prophylactic antibiotic will be administered prior to the urodynamic test.

The investigator or fully trained designated study personnel will always be present to conduct the clinical study and may terminate the study at their discretion based on changes in subject condition and study observations.

9 STUDY POPULATION

Study subjects will include female patients with an implantable PNS device. To be eligible to participate in this study, an individual must meet all of the inclusion criteria and none of the exclusion criteria listed below.

9.1 Inclusion Criteria

1. Women between the ages of 18 and 85 years old, inclusive.
2. Implanted with a neurostimulation device for at least 3 months prior to consent (Medtronic InterStim neurostimulator models 3023, 3058, 97810, or similar;)
3. Implanted with a tined lead that is placed and functionable at the pudendal nerve (Medtronic model 3889 or similar)
4. Is capable of understanding clinical study procedures and giving informed consent.
5. Willing and able to visit the clinic for the UDT evaluation (study procedure)

Note: No more than eight subjects having no history of SUI as determined by the investigator.

9.2 Exclusion Criteria

1. Medically unstable at time of study and unsafe to undergo urodynamic testing as determined by the investigator
2. Active bladder cancer
3. History of pelvic radiotherapy
4. Active gross hematuria
5. Active symptomatic urinary tract infection (UTI)
6. Active symptomatic uncontrolled bladder instability as determined by the investigator
7. History or symptoms of cystocele, enterocele or rectocele of grade 3 or 4. Per the medical record or as determined by the investigator
8. Presence of an artificial urinary sphincter
9. Women who are pregnant and/or have given birth in the previous 12 months
10. Any medical condition (e.g. Multiple Sclerosis, spinal cord injury, mobility) or uncontrolled chronic disease (e.g. diabetes, renal diseases that requires dialysis) that would interfere with the patient's ability to comply with the protocol and/or may affect the outcome of this study or safety of the subject as determined by the investigator
11. BMI>39

9.3 Enrollment

The point of enrollment is defined as the time a participant signs the ICF and meets all the inclusion criteria and none of the exclusion criteria.

9.4 Screen Failure

Participants who are consented to participate in this early feasibility clinical trial are considered screen failures if the subject does not meet one or more of the eligibility criteria required for participation. Screen failures will not be assigned to the study procedure and their data will not be included in the data analysis.

Screen failure because of Exclusion criterion #1 (i.e. unstable medical condition) may be rescreened. Rescreened participant should be assigned the same participant number as for the

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initial screening.

9.5 Participant Discontinuation/Withdrawal from the Study

Study participants are free to withdraw from participation in the study at any time upon request.

Although Investigators should seek to minimize participant discontinuation or withdrawal from the study except for safety reasons. The PI may discontinue or withdraw a study participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires withdraw from participation
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The study participant is unable to receive PNS

The reason for participant discontinuation or withdrawal from the study will be recorded on the Study Exit Case Report Form (CRF). Subjects who sign the Informed Consent Form but did not completed the UDT with and without PNS may be replaced.

9.6 Lost to Follow-Up

A participant will be considered lost to follow-up if the participant fails to return for the stimulation visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within one week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the participant where possible, three telephone calls, text or any other messaging methods. These contact attempts should be documented in the participant's medical record or study file.

10 Data Analysis

This early feasibility study is designed to obtain initial insights into evaluating the device design concept with respect to initial clinical safety and device functionality. In general, feasibility studies are not designed or intended to generate statistically valid results. Therefore, 1) there will be no formal statistical hypothesis testing conducted, and 2) sample size is not based on power calculations.

This study is designed to gather information about the pressure waveform parameters during leak point pressure events in urodynamic testing. UDT data will be collected and analyzed to assess the changes and dynamic in LPP, UPP and other UDT parameters with and without acute PNS.

The results of this study may be used to design a statistically powered study to demonstrate safety and efficacy of the new therapy. A sample size of up to 15 will allow initial assessment of safety and improve understanding how LPP changes with acute PNS.

10.1 General Approach

In this study, only subjects that receive PNS will be included in the analysis. Study subjects that receive acute PNS and complete the UDT will be assessed for safety and evaluation of the changes in LPP and UPP with and without PNS. Study subjects that receive acute PNS and do not completed the UDT will be included in safety analysis only. Study subjects that do not receive acute PNS will be excluded from the study analysis.

Data analysis will comprise of descriptive statistics (means, standard deviations, correlations, etc.) on the outcome measures and variables listed in **Error! Reference source not found.** below.

The final report will include summary data and descriptive statistics of measurements performed in the study, including all Adverse Events and complications reported during the urodynamic test.

TABLE 1: DATA SET VARIABLES

Category	Variables
General	• Informed Consent (date, version, process)
Demographics	• Year of birth (age at time of test) • Gender • Ethnicity • Race • BMI (Height, Weight)
Medical history:	• Condition • Onset year
Urinary incontinence history:	• Type (SUI, UUI, MUI, Other) • Duration • Treatment • Severity (number of incontinence episodes/day)
Eligibility	• Inclusion criteria • Exclusion criteria
Neurostimulator	• Manufacturer • Model numbers of components • Indication • Stimulation setting/parameters • Electrode configuration

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Urodynamic test*	• Test date • Post voiding residual • Fill-in rate • Bladder volume at 1st instability event • Detrusor pressure at 1st instability event • Bladder volume at leakage event • Detrusor pressure at leakage event • Max detrusor pressure during filling phase • Max cystometric capacity • Cough Leak Point Pressures (CLPP) • Valsalva Leak Point Pressures (VLPP)
Neurostimulation settings	• Existing neurostimulator settings • Neurostimulator settings during setup and testing • Patient sensations during stimulation, including the location and intensity of the sensation
Electromyography	• Number of electrodes • Location of electrodes
Urethral pressure profile (optional)	• Urethral Closure Pressure Profile (UCPP) • Maximum Urethral Closure Pressure (MUCP)

10.2 Safety Analyses

All subjects that received acute PNS will be included in the safety analysis. The rate of serious study related adverse events will be summarized as the number of events, the number of subjects with event and the percent of subjects with event within the safety population. There are no formal statistical hypothesis tests. Additionally, the number of all study related AE, the number of subjects with study related AE and the percent of subjects with AE will be summarized by type of event, severity, seriousness and relationship to the study.

10.2.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a study subject whether or not considered related to the study device, study procedures or study requirements that is identified or worsens during the study.

Adverse events must be assessed and documented by the investigator at the time of the study procedure visit.

The Investigator should institute appropriate therapeutic and follow-up measures in accordance with good medical practice and record them in the subject's medical history.

All AEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedure (assessed only by those with the training and authority to make an assessment), and time of

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resolution/stabilization of the event.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the procedure visit, it will be recorded as an AE.

A list of possible risks associated with the study procedure are included in the section titled "Known potential risks" within this document.

10.2.2 Serious Adverse Events (SAE)

A Serious Adverse Events (SAE) is defined as any adverse event that:

- Resulted in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in permanent impairment of a body structure or body function
- Requires medical or surgical intervention to prevent permanent impairment to body structure or a body function
- Led to fetal distress, fetal death or congenital abnormality or birth defect.

A written report will be provided to the IRB/EC per the IRB/EC's reporting guidelines.

10.2.3 Device Deficiencies or Complaints

All problems/deficiencies related to the neurostimulator's physician programmer and to the urodynamic machine (study equipment) will be documented and reported to the Sponsor but are not to be classified as an adverse event in the absence of a subject harm. However, if there is an adverse event that results from the study equipment failure, user error, or malfunction or any other study specific equipment failure or malfunction, that specific event would be classified as an adverse event and reported. If that failure or harm is not previously identified, it is considered unanticipated.

Since the study procedure includes resetting of the PNS parameters, optimization of pudendal nerve stimulation is not considered adverse events but rather part of the anticipated investigation. However, if the stimulation lead polarity assignment and/or adjusting stimulation current parameters result in patient harm, then this is a study procedure related adverse event further categorized as related to Study Equipment (excluding the neurostimulator's physician programmer or UDT systems).

Study specific equipment failures and malfunctions should also be documented in the subject's medical record.

10.2.4 Classification of an Adverse Event

A. Severity of event

The following guidelines will be used to describe severity.

- **Mild** – No major impact to the Subject. Events require minimal or no treatment and do not interfere with the participant's daily activities, when applicable.
- **Moderate** – Events result in a low level of inconvenience or concern to the subject. Moderate events may cause some interference with functioning.

- **Severe** – Substantial disruption to Subject well-being. Events interrupt a participant's usual daily activity and may require intervention. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

B. Relationship to event

All AEs must have their relationship to study procedure assessed by the clinician who examines and evaluates the participant based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect. However, in this study there is no study product. The study procedure includes standard UDT and a modified PNS. When assessing relationship of the AE to the study procedure the assessing clinician should ask if the UDT and/or the acute PNS caused the AE.

- **Related** – The AE is known to occur with the study procedure, there is a reasonable possibility that the study procedure caused the AE, or there is a temporal relationship between the study procedure and event. Reasonable possibility means that there is clear evidence to suggest a causal relationship between the study procedure and the AE, and other possible contributing factors can be ruled out.
- **Potentially Related** – There is some evidence to suggest a causal relationship or an equally or more likely than not related relationship exists (e.g., the event occurred within a reasonable time after the study procedure). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "Potentially Related" upon discovery, the AE can be flagged as requiring more information and later be changed to "Related" or "Not Related", as appropriate.
- **Not Related** – There is not a reasonable possibility that the administration of the study procedure caused the event, there is no temporal relationship between the study procedure and event onset, or an alternate etiology has been established for the event.

10.2.5 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of (S)AE may come to the attention of study personnel during study visits, or upon review by a study monitor. All AEs occurring during the study must be documented appropriately regardless of relationship.

The Principal Investigator will record all reportable events with start dates occurring during the acute stimulation visit. All study related AEs will be followed until 7 days after the end of the study.

All SAEs, and UADEs will be followed until the event is resolved or until a final outcome is established by the Principal Investigator, or for no more than 30 days post the end of the study, whichever occurs first.

Device Deficiencies or Complaints related to any of the market released medical devices utilized during the study or during the clinically indicated procedure should follow standard reporting procedures applicable to device user facilities.

10.2.6 Reporting Events to Participants

Study participants will be informed about AEs and SAEs where that information may be relevant to their participation in the study or during their participation in the study, such as correct operation of ambulatory equipment.

10.2.7 Unanticipated Problems

A. Unanticipated Adverse Device Effect (UADE)

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with the study device if that effect, problem or death is not previously identified in nature, severity or degree of incidence in this investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

In the event of a UADE, the research site staff will notify the IRB/EC as soon as possible. A written report will be provided to the IRB/EC within their reporting guidelines.

B. Reporting Unanticipated Problems to Participants

Study participants will be informed about Unanticipated Problems where that information may be relevant to their participation in the study or during their participation in the study, such as the correct operation of ambulatory equipment.

11 Supporting documentation and operational considerations

11.1 Study oversight and integrity

The Investigator/Sponsor is committed to ensuring that the data are generated, documented and reported in compliance with ICH-GCP, the protocol and the applicable regulatory requirements.

11.2 Institutional Review Board (IRB)

The Investigator will seek IRB approval before the final protocol is implemented.

11.3 Protection of Human Subject (Informed Consent/Process)

Patients will be required to sign an Informed Consent prior to preforming any study specific activity.

To obtain Informed Consent in compliance with the Regulations (21 CFR § 812 and § 50, 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56 and ICH-GCP) each patient must be fully informed about the investigation, including;

- An explanation of the study procedure;
- The potential risks and/or discomforts;
- The potential benefits;
- Information regarding whom to contact for answers about the study and their rights as a research participant;
- An explanation that participation is voluntary and they can withdraw from the study at any time without prejudice.

Informed Consent shall be provided to the patient in a language that they can read and understand. The Informed Consent forms must include the elements of Informed Consent as required by 21 CFR § 50, Protection of Human Subjects and must be approved by the reviewing IRB.

After the information contained in the Informed Consent documents has been reviewed with each patient, the patient must sign and date the document, indicating willingness to be screened or participate in the clinical study. The investigator or study personnel designated to administrate Informed Consent must sign and date the form. A copy of the signed Informed Consent documents will be given to the patient. The signed Consents should be kept in the hospital/clinic patient file; a copy of the signed consent forms should be placed in the study e-file.

Subjects will be informed if new information becomes available in the course of the study, which may influence a subject's willingness to participate in the study.

The site Principal Investigator is responsible for ensuring proper consenting procedures are followed in this study. The responsibility for performing the consent process may be delegated by the site Principal Investigator to site staff who should have received study training.

The site may use of electronic systems and processes that may employ multiple electronic media to obtain informed consent FDA's requirements for electronic records/electronic signatures, informed consent, and IRBs as set forth in 21 CFR parts 11, 50, and 56, respectively.

11.4 Study Discontinuation and Closure

This study may be prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated, the Investigator PI will promptly inform study participants, and the Institutional Review Board (IRB), and will provide the reason(s) for the termination. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete or evaluable
- The determination that the primary endpoint has been met
- Determination of futility
- An enrollment rate far below expectation that prejudices the conclusion of the study

The study may be discontinued at any time by the IRB as part of their duties to ensure that research participants are protected.

11.5 Confidentiality and Privacy

Participant confidentiality and privacy are strictly held in trust by the Investigator and the clinical research staff. This confidentiality includes the results of any clinical testing and the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

Confidentiality of subject data will be maintained at all times, and any subject information needs

to be de-identified by the participating institution. All documentation relating to a subject will be kept in a secure location.

The site will ensure that the study outcome will not contain any patient identifying data other than the subject ID, which is a unique identifier that links a study subject to his or her medical records at the participating study site. Information will not be released without the written permission of the participant, except as necessary for monitoring by the IRBs, or other regulatory agencies.

All research activities will be conducted in as private a setting as possible.

The study participant's contact information will be securely stored at the site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies and requirements.

This is a paperless study. The study data entry and study management systems used by the site's research staff will be secured, and password protected within the study EDC system. At the end of the study, all study databases will be de-identified and archived.

11.6 Safety Oversight

This is an early feasibility study designed to gather initial information assessing the changes in LPP and UPP during acute PNS utilizing commercially released, market approved devices. Both the UDT system (Laborie, Sweden) and the implantable neurostimulator (Medtronic, USA;) have been approved by the FDA for their respective indications. The study does not include any invasive nor experimental interventions/treatment. The participating subjects already received the IPG per indication and the urodynamic test is a well-established, verified and institutional standard of care study/test to evaluate the urine storage and release cycle.
Furthermore, the participating sites will have sufficient expertise in managing clinical studies in general and urodynamic testing in particular. The chosen PIs will be qualified investigators who specialize in implanting urology neurostimulators and with adequate study training.
Therefore, there is no Clinical Event Committee (CEC) nor Data Safety Monitoring Board (DSMB) for this study. Yet, an internal safety team comprised of the Investigator and the clincial trial manager will evalute safety data as soon as the event is reported. All safety information will be collected, analyized and reported for all eligible subjects who complete UDT during acute PNS cycle.

11.7 Study Forms

Case Report Forms (CRF) will be used to collect study data. CRFs must accurately reflect the data on the patient's chart and the patient's experience.

The electronic records, such as the CRFs and study regulatory documents, will be encrypted and secured with password protection. The database will only contain de-identified subject information. Electronic communication with outside collaborators will involve only unidentifiable information.

All subject related data should be entered and e-signed and dated by the investigator. Every attempt should be made to obtain requested information. However, if a question does not apply, enter N/A (Not Applicable) in the Comment Section. Corrections are tracked by the system and the reason for the change should be given to any change to the data.

11.8 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, ICH GCP, or site's SOP requirements.

The investigator will indicate whenever a requirement of the protocol has not been met, using the Protocol Deviation CRF. It is the responsibility of the Investigator to use continuous vigilance to identify and report deviations. All protocol deviation will be reported to the IRB within 5 working days of the deviation.

Protocol Deviations may include but are not limited to:

- Failure to obtain informed consent
- Deviation of the informed consent process
- Not meeting inclusion/exclusion criteria
- Missing required data

All deviations must be reported. The site investigator is responsible for knowing and adhering to their IRB protocol deviations reporting requirements.

11.9 Publication and Data Sharing Policy

This study is designed to gather and report clinically relevant information for the advancement of patient care. It is intended that peer-reviewed publications/abstracts will be generated to report the primary study results.

Study results will be in aggregate form only. Patient's identity will not be publicly disclosed.

12 Abbreviations

The list below includes abbreviations utilized in this protocol:

AE	Adverse Event
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CRF	Case Report Form
EC	Ethics Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IC	Interstitial Cystitis
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intention-To-Treat
MUI	Mixed Urinary Incontinence
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SUI	Stress Urinary Incontinence
US	United States
UUI	Urge Urinary Incontinence

13 References

1. Aoki Y, Brown HW, Brubaker L, Cornu JN, Daly JO, Cartwright R. Urinary incontinence in women. Nat Rev Dis Prim 2017;3(25):17042
2. Hunskaar S, Arnold EP, Burgio K, Diokno AC, Herzog AR, Mallett VT. Epidemiology and natural history of urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2000;11(5):301–19
3. Jonsson Funk M, Levin PJ, Wu JM. Trends in the surgical management of stress urinary incontinence. Obstet Gynecol 2012;119(4):845–51
4. Shamliyan T, Wyman J, Bliss DZ, Kane RL, Wilt TJ. Prevention of urinary and fecal incontinence in adults. Evid Rep Technol Assess (Full Rep) 2007;(161):1–379.
5. Tennstedt SL, Fitzgerald MP, Nager CW, et al. Quality of life in women with stress urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2007;18(5):543–9.
6. Hägglund D, Walker-Engström ML, Larsson G, Leppert J. Quality of life and seeking help in women with urinary incontinence. Acta Obstet Gynecol Scand 2001;80(11):1051–5.
7. Subak LL, Brubaker L, Chai TC, et al. High costs of urinary incontinence among women electing surgery to treat stress incontinence. Obstet Gynecol 2008;111(4):899–907
8. Wilson L, Brown JS, Shin GP, Luc KO, Subak LL. Annual direct cost of urinary incontinence. Obstet Gynecol 2001;98(3):398–406
9. Robinson D, Cardozo L. Treatment options for stress urinary incontinence. Pelvic Floor Dysfunct Pelvic Surg Elder An Integr Approach 2017;6(Table 1):185–94
10. Neumann PB, Grimmer KA, Deenadayalan Y. Pelvic floor muscle training and adjunctive therapies for the treatment of stress urinary incontinence in women: A systematic review. BMC Womens Health 2006;6
11. Brown ET, Reynolds WS, Kaufman MR, Dmochowski RR. Advances in the Treatment of Urinary Incontinence in Women. Clin Med Insights Urol 2015;8:CMU.S13181
12. Blok B, Van Kerrebroeck P, de Wachter S, et al. A prospective, multicenter study of a novel, miniaturized rechargeable sacral neuromodulation system: 12-month results from the RELAX-OAB study. Neurourol Urodyn 2019;38(2):689–95
13. Peters KM, Feber KM, Bennett RC. Sacral versus pudendal nerve stimulation for voiding dysfunction: A prospective, single-blinded, randomized, crossover trial. Neurourol Urodyn 2005;24(7):643–7
14. Chancellor MB, Chartier-Kastler EJ. Principles of Sacral Nerve Stimulation (SNS) for the Treatment of Bladder and Urethral Sphincter Dysfunctions. Neuromodulation 2000;3(1):16–26
15. Peters KM. Neuromodulation for the treatment of refractory interstitial cystitis. Rev Urol 2002;4 Suppl 1:S36-43
16. Meyer S, Kuntzer T, De Grandi P, Bachelard O, Schreyer A. Stimulated pressure profile at rest: a noninvasive method for assessing urethral sphincter function. Urology 1998;52(4):679–84
17. Gray M. Traces: making sense of urodynamics testing--part 7: Evaluation of bladder filling/storage: Evaluation of urethral sphincter incompetence and stress urinary incontinence. Urol Nurs 2011;31(5):267—77, 289
18. Pizzoferrato A-C, Fauconnier A, Fritel X, Bader G, Dompeyre P. Urethral Closure Pressure at Stress: A Predictive Measure for the Diagnosis and Severity of Urinary Incontinence in Women. Int Neurourol J 2017;21(2):121–7