Study Title: Clinical Study of Neuspera's Implantable Sacral Nerve Stimulation (SNS) System in Patients with Symptoms of Urinary Urgency Incontinence (UUI)

Document: Clinical Investigation Plan / Study Protocol

Protocol No. NSM-004
Version 21.0
04 Apr 2025

NCT number: NCT04232696

Clinical Study of Neuspera's Implantable Sacral Nerve Stimulation (SNS) System in Patients with Symptoms of Urinary Urgency Incontinence (UUI)

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Confidentiality Statement:

The information provided in this document is strictly confidential and may not be disclosed to parties other than study personnel, appropriate governmental and regulatory agencies and the Institutional Review Board or Ethics Committee directly involved with this study. All parties must understand that confidential information may not be disseminated further without prior written permission from Neuspera Medical Inc.

SPONSOR SIGNATURE PAGE

Title: Clinical Study of Neuspera's Implantable Sacral Nerve Stimulation (SNS) System in Patients with Symptoms of Urinary Urgency Incontinence

Protocol ID: NSM-004

Sponsor's statement

I, the Sponsor, have reviewed this clinical investigation plan describing the design and specific provisions of the clinical investigation. I agree with the content of this document.

Mark Vollmer	Director of Clinical Research
Sponsor representative name (print)	Title
DocuSigned by: Mark Vollmer 9E20427ACEEB4E3...	2025-Apr-04
Signature	Date

INVESTIGATOR SIGNATURE PAGE

Title: Clinical Study of Neuspera's Implantable Sacral Nerve Stimulation (SNS) System in Patients with Symptoms of Urinary Urgency Incontinence

Protocol ID: NSM-004

Investigator's statement

I agree to conduct this study in accordance with the design and specific provisions of this protocol; modifications to the study are acceptable only with a mutually agreed upon protocol amendment as approved by the Sponsor and the Institutional Review Board or the Ethics Committee. I agree to await Institutional Review Board or Ethics Committee approval of the protocol and informed consent before initiating the study, to obtain consent from subjects prior to their enrollment in the study, to collect and record data as required by the protocol and case report forms, and to maintain study documents for the period of time required.

Confidential

This document contains confidential information belonging to Neuspera Medical Inc. except as may be otherwise agreed to in writing, by accepting or reviewing these materials, I agree to hold such information in confidence and not to disclose it to others (except where required by applicable law), nor use it for unauthorized purposes.

Investigator name (print)

Signature Date

SYNOPSIS

Clinical investigation plan	
Title	Clinical Study of Neuspera's Implantable Sacral Nerve Stimulation (SNS) System in Patients with Symptoms of Urinary Urgency Incontinence
Short title	SANS-UUI
Protocol ID	NSM-004
Investigational device	
Name	Neuspera's Implantable Sacral Nerve Stimulation (SNS) System
Description	Miniature wireless midfield powered implanted neurostimulation device for urinary urgency incontinence (UUI).
Indications statement	Neuspera's Implantable SNS System is indicated to treat subjects with UUI who have failed or could not tolerate more conservative treatments.
Sponsor	
Name	Neuspera Medical Inc.
Contact details	Neuspera Medical Inc. 51 Daggett Drive San Jose, CA 95134, USA Telephone: +1 408.612.7570
Investigation centers	
Number of centers	The study was designed to be conducted in two Phases. The enrollment period for Phase I has been completed. Phase I was conducted in 11 clinical study sites in the US and Europe. Phase II of the study will be conducted in up to 35 clinical sites in the US, Canada and Europe, inclusive of the Phase I centers who participate in Phase II. Phase I sites unable to participate in Phase II will not count towards Phase II site limits. It is expected that no more than 5 sites to be included from Europe and Canada. More than 50% of the subjects enrolled will be from the United States.
Location of centers	United States, Canada, and Europe
Coordinating Investigator for the SANS-UUI Study	
Contact details	Osvaldo Padron, MD Florida Urology Partners, LLP 5913 Webb Rd Tampa, FL 33615 Office: (813) 875-8527 x2106
Clinical investigation design	
Objective	The trial is designed in two phases: Phase I and Phase II. The objective of Phase I was to assess the utilization of the system during the SNS trial and follow-up periods and to help inform the length of hours of daily stimulation to be used in Phase II of the trial.

	The objective of Phase II is to assess the safety and efficacy of the Neuspera SNS System at 6-months for the primary efficacy endpoint and at 6 and 12 months for secondary safety and efficacy endpoints. As Phase II is designed with a Modified Intent-to-Treat analysis (mITT), all implanted subjects will be followed to the endpoint determination.
Design	Prospective, multi-center, single-arm, seamless phased-pivotal study conducted in subjects diagnosed with UUI who have failed or could not tolerate more conservative treatment. The trial will be conducted in two phases: <u>Phase I</u> In Phase I, the trial was designed to allow the enrollment of up to 55 subjects. An enrolled subject is one who signed the informed consent and an implant with the Neuspera neurostimulator system ("system") was attempted. A total of 39 subjects were enrolled in Phase I. As designed subjects who failed to achieve an appropriate motor response during intra-operative testing were considered enrolled but were not implanted and exited from the study. A total of 5 subjects failed to achieve an appropriate motor response in Phase I of the trial. The design of the study allowed for the system to be trialed for approximately 21 - 49 days in implanted subjects. Subjects had an initial trial period of 21 days with 2-hours of daily stimulation using the external Wireless Transmitter. At the end of a subject's trial phase, treatment efficacy was assessed. Those subjects with acceptable efficacy (≥50% reduction in number of UUI episodes) were considered responders and proceeded into the post-trial follow-up period with 2-hours of daily stimulation using the Wireless Transmitter. Those with less than acceptable efficacy (<50% reduction in number of UUI episodes) proceeded for an additional trial period with 4-hours of daily stimulation with the Wireless Transmitter for 14 days. After 14 days of 4-hours of daily stimulation those subjects with ≥50% reduction in number of UUI episodes were considered responders and proceeded into the post-trial follow-up period with 4-hours of daily stimulation. The study was designed such that those with <50% reduction in number of UUI episodes were to proceed into a third trial period with 8-hours of daily stimulation with the Wireless Transmitter for 14 days. After 14 days of 8-hours of daily stimulation, those subjects with ≥50% reduction in number of UUI episodes were to be considered responders and would then proceed into the post-trial follow-up period with 8-hours of daily stimulation. For those subjects who did not respond to SNS therapy, alternative treatments were to be discussed with the Investigator and the Neuspera neurostimulator was to be explanted. Neuspera's Wireless Transmitter(s), Wireless Transmitter Charging Pad, and Patient Controller were to be returned to the investigational center and the subject was to have a 30-day follow-up visit for safety purposes. The subject would then be exited from the study.

Of the 34 subjects implanted with the neurostimulator, only one subject was a non-responder after 2-hours of daily stimulation. This subject was a responder after an additional 14-days at 4 hours of daily stimulation and continued into the post-trial follow-up phase. There have been twelve device explants in the trial and two subjects exited the trial without device explant (one due to lost-to-follow-up, one due to an adverse event of dementia). Eleven subjects requested explant due to therapy not producing desired effect or unsatisfied with therapy or device performance, and one subject was explanted due to non-compliance.

Phase I responders will continue to be followed until US PMA approval. European approval, CE Mark, may be achieved earlier or later than PMA approval is achieved which may be 36 months or longer post trialing period for some subjects; however, all subjects will be followed until US PMA approval. If Neuspera determines that regulatory approval will not be achieved, the trial will be closed. If regulatory approval is achieved, the subjects may be approached to continue participation in a post market clinical study and will be provided a separate informed consent at that time.

Phase I Sub-Study: There is a sub-study to investigate the effectiveness and subject acceptance of half-hour daily stimulation to treat UUI. The details are provided in Appendix A: Phase I Sub-Study.

<u>Phase II</u>

A group of up to 255 subjects (independent of subjects enrolled in Phase I of the trial) will be enrolled. The definition of enrollment for Phase II is modified from the definition used in Phase I. An enrolled subject in Phase II is one who signed the informed consent. Subjects who pass all pre-implant screening criteria will be scheduled for implant. Enrollment will be stopped after reaching 120 attempted implants; the implant success rate is expected to be 95%. Subjects who are already enrolled after the last attempted implant will be allowed to be implanted. All subjects who successfully complete intraoperative testing will be implanted with the neurostimulator. In the first 28 days subjects will receive 2 hours of continuous daily stimulation using the external Wireless Transmitter. At the end of 28 days of treatment, efficacy will be assessed. Subjects with acceptable efficacy (≥50% reduction in number of UUI episodes) will be considered a responder and will continue in the post-implant follow-up with 2 hours of daily stimulation using the Wireless Transmitter. Those with less than acceptable efficacy (<50% reduction in number of UUI episodes) will continue for an additional 14-day period with 4 hours of daily stimulation with the Wireless Transmitter. After 14 days of 4 hours

	of daily stimulation those subjects with ≥50% reduction in number of UUI episodes will be considered responders. Those subjects who increased to 4 hours of daily stimulation, regardless of responder or non-responder status at the end of the 42-day period will continue in the post-implant follow-up with 4 hours of daily stimulation. A decision to continue a subject with less than a 50% improvement at the end of the 42-day period will be made by the investigator based on what they determine is in the best interest of the subject. A subject may withdraw their consent from participation at any time regardless of responder status. As commercial sacral neurostimulation therapies report responder rates at 1-month post implant or following a trial period with an implanted lead connected to an external stimulator, the responder rate at day 28 or day 42 clinic visit post-implant will be used as a comparison point for SNS trial therapy success with current clinical literature. All implanted subjects will be followed for efficacy and safety with the primary endpoint assessed at the 6-month follow-up visit. Subjects will be assessed again for safety and efficacy at 12 months post-implant for secondary endpoints in the trial. The sponsor intends to file a PMA submission at the end of the six-months of follow-up if the primary endpoint is achieved. Phase II subjects will continue to be followed through 12 months and until US PMA approval. Health Canada approval, European approval, CE Mark, may be achieved earlier or later than PMA approval.
Arms and interventions	Single-arm clinical study
Follow-up visits	In Phase I, all subjects will return to the clinic for monthly visits up to 6 months for post-trial procedures and every three months through the 12-month post-trial visit, and then every six months thereafter until regulatory approval is achieved, estimated to be up to 60 months. In Phase II, enrolled subjects will return to the clinic for monthly visits up to 6 months for post-implant procedures and every three months through the 12-month visit, and then every six months thereafter until regulatory approval is achieved, estimated to be up to 36 months.
Total duration	The total expected duration of the clinical trial is dependent on the length of time to regulatory approval. All implanted subjects in Phase I and Phase II will continue to be followed until US PMA approval. Health Canada approval, European approval, CE Mark, may be achieved earlier or later than PMA approval. If achieved earlier, all Canadian and EU subjects will continue to be followed until US PMA approval is achieved which may be 60 months or longer for some subjects. Subjects enrolled earlier will have a longer follow-up than subjects enrolled later. In Phase II, subjects enrolled later may be followed for less than 36 months but at least until

	the 12-month follow-up visit is completed. It is estimated that the first subjects implanted in Phase I will be in the study approximately 5 years. If Neuspera determines regulatory approval will not be achieved, the study will be closed.
Primary Efficacy Endpoint (Phase II)	The primary efficacy endpoint is defined as the percentage of all implanted subjects who experience an improvement in UUI symptoms of at least 50% or more (therapy responders). A therapy responder is defined as experiencing ≥50% reduction in the number of UUI episodes at 6 months post-implant, relative to the number of UUI episodes at baseline. Statistical evaluation will be based on a comparison of the percentage of responders to a performance goal of 50%. Calculation of the primary efficacy endpoint will be based on the mITT analysis set.
Safety endpoints (Phase II)	The primary safety endpoint is defined as the incidence of device-related SAEs through the 6-month post-implant visit. The analysis of the endpoint is the proportion of subjects experiencing a device-related SAE through the 6-month post-implant.
Secondary Endpoints	The secondary endpoints include the following, assessed at both the 6 and 12 months post implant visits unless specified otherwise: • Change from baseline in quality of life as measured and assessed by the total ICIQ-OABqol score. • Change from baseline in mean number of UUI episodes. • The percentage of subjects who experience an improvement in UUI symptoms (therapy responders) of at least 50% or more at 12-month visit post-implant. • The percentage of subjects who experience an improvement in ICIQ-OABqol of at least 10 points. • Change in urgent voids per day calculated across all diary episodes with at least mild urgency. • Change in average number of daily voids from baseline in subjects with at least 8 voids at baseline. • Change in quality of life measured from baseline as measured and assessed by the ICIQ-OABqol subscale scores. • Comprehensive summary of all adverse events (AEs) for the duration of study participation. • Device parameters including but not limited to voltage, pulse width, frequency, and stimulating electrode. • Physician and subject satisfaction as assessed with the User Experience Questionnaire at 6-month visit post-implant. • Change in Male/Female Lower Urinary Tract Symptoms questionnaire.

	• The percentage of subjects with device-related serious adverse events reported through 12-month visit post-implant. • Change in total urinary output as measured by 72-hour bladder diary. • Change in fecal incontinence as measured by the Wexner Scale compared to baseline. Calculated in subjects with fecal incontinence. • Patient Global Impression of Improvement (PGI-I) measured after implant during follow-up.
Secondary Endpoints That May Be Used for Labeling Claims (Phase II)	The following secondary endpoints will be included in a hierarchical analysis of study endpoints and may be intended for labeling claims (all at 6-month visit post-implant follow-up): • Change from baseline in mean number of UUI episodes • Change from baseline in ICIQ-OABqol score • The percentage of subjects who experience an improvement in ICIQ-OABqol of at least 10 points • Change in urgent episodes per day from baseline. Calculated across all diary episodes with at least mild urgency • Change in average number of daily voids from subjects with at least 8 voids at baseline • Change in fecal incontinence as measured by the Wexner Scale compared to baseline. Calculated in subjects with fecal incontinence. The type I error for the primary efficacy endpoint and for this subset of secondary endpoints will be controlled via hierarchical testing. Performance goals for each hypothesis and other statistical details are provided in the Statistical Analysis Plan (SAP).
Clinical investigation population	
Sample size	The study will be conducted in two operationally seamless phases: Phase I and Phase II. In Phase I, the trial was designed to allow the enrollment of up to 55 subjects and a total of 39 subjects were enrolled. It was anticipated that approximately 40 of the enrolled subjects would have an appropriate motor response during intra-operative testing and would be implanted. A total of 5 subjects failed to achieve an appropriate motor response in Phase I of the trial and were exited from the study. A total of 34 enrolled subjects were implanted with the Neuspera neurostimulator. It was estimated that approximately 33% of the implanted subjects would be determined as non-responders or would drop out of Phase I for other reasons following the sacral nerve stimulation (SNS) trial period. Thus, approximately 27 subjects were to continue in the post-trial period. A total of 34 enrolled subjects were implanted with the Neuspera neurostimulator and all 34 subjects continued into the follow-up phase of the trial.

	In Phase II of the trial, the pivotal phase, up to 255 may be enrolled (consented). It is anticipated that approximately 43% of subjects may be screen failures and that the implant success rate will be approximately 95%. Enrollment will be stopped after reaching 120 attempted implants, resulting in approximately 114 successful implants. Revisions will not count towards attempted implants. Subjects who are already enrolled after the last attempted implant will be allowed to be implanted. The primary efficacy endpoint will be assessed in all subjects for whom an initial implant is attempted. Missing data at 6 months will be imputed.
Inclusion criteria	General Inclusion Criteria: 1. Is willing and able to understand and has voluntarily signed and dated the current approved informed consent. 2. Is male or female 22 years of age or older. 3. Has a Body Mass Index (BMI) greater than or equal to 18 and less than or equal to 40 kg/m^2. 4. Is a good surgical candidate and is capable of participating in all testing and follow-up clinic visits associated with this clinical study and is capable of independently using the system components as described in the Patient Manual. 5. Is ambulatory and able to use toilet without assistance. 6. Has a diagnosis of UUI for greater than or equal to 6 months prior to the screening baseline visit date. 7. Has typical residual bladder volume < 150 cc tested within 6 months prior to the screening baseline visit date or is willing to have a test at screening baseline visit. 8. Has urodynamic testing (uroflowmetry, cystometry, and pressure flow) completed within 6 months prior to the screening baseline visit date or is willing to have testing at the screening baseline visit. 9. Has cystoscopy testing completed within 6 months prior to the screening baseline visit date or is willing to have a test at the screening baseline visit. 10. Has failed or was not a candidate for more conservative treatment (e.g, pelvic floor exercise, biofeedback, behavioral modification). 11. Has failed, could not tolerate (stopped taking medication due to lack of efficacy or intolerable side effects), or not a good candidate for (as determined by treating physician) at least one (1) antimuscarinic or β3 adrenoceptor agonist medication. 12. Is willing and able to washout (at least five half-lives) from OAB medications for a period determined appropriate based on type of OAB medication prior to the baseline bladder diary and remain off OAB medications through the 12-month follow-up visit. 13. Has appropriate sacral anatomy as determined by sponsor's and investigator's analysis of radiographic imaging. (The distance

	from the surface of the skin in the prone and seated position to the bone edge of the S3 foramen must be within the capabilities of the system). Baseline Bladder Diary Inclusion Criteria: 14. Has a diagnosis of UUI with at least 4 UUI episodes on a 72-hour diary, and minimum of one (1) UUI episode per 24-hour period.
Exclusion criteria	**General Exclusion Criteria:** 1. Has a hemoglobin A1c of >8% or has diabetes mellitus with glucosuria. 2. Has diabetic neuropathy. 3. Has interstitial cystitis or bladder pain syndrome as defined by either American Urological Association (AUA) or European Association of Urology (EAU) guidelines, chronic pelvic pain, or recurrent symptomatic urinary tract infections. 4. Has skin, orthopedic, neurological, or hematological (bleeding disorder) or anatomical limitations that could prevent successful placement of the neurostimulator. 5. Has broken, blistered skin or compromised circulation in the area of the neurostimulator implant. 6. Has neurogenic bladder dysfunction such as traumatic or atraumatic myelopathy, multiple sclerosis, Parkinsonism, or history of cerebrovascular accident. 7. Has documented urinary retention within 6 months prior to the screening baseline visit date. 8. Has clinically significant bladder outlet obstruction. 9. Is currently undergoing or has previously undergone pelvic irradiation. 10. Is a subject with a mechanical obstruction such as benign prostatic hypertrophy, urethral stricture, or cancer. 11. Has current grade 3 or 4 pelvic organ prolapse including cystocele, rectocele, enterocele, procidentia or vaginal vault prolapse. 12. Has symptomatic urinary tract infection (UTI); the subject may be considered for study enrollment if the subject is symptom-free after a full course of treatment prior to beginning the baseline bladder diary. If an asymptomatic bacteriuria is detected during the urinalysis performed at screening, a subject may be enrolled without a waiting period relative to UTI treatment. 13. Has primary stress incontinence or mixed incontinence where the stress component predominates or has been treated surgically for stress urinary incontinence within 6 months prior to the screening baseline visit date.

	14. Has received tibial nerve stimulation (TNS) in the past 3 months for the treatment of overactive bladder or unwilling to stay off TNS therapy for 12-month period following implant. 15. Has received treatment of urinary symptoms with any botulinum neurotoxin type-A (BoNT-A) agent in the past 12 months; (e.g. obotulinumtoxinA, Botox,® abobotulinumtoxinA, Dysport® IncobotulinumtoxinA, Xeomin®). 16. Is a woman who is pregnant or planning to become pregnant during this clinical study or is a woman of child-bearing potential who is not using a medically acceptable method of birth control. Women of child-bearing potential must undergo a pregnancy test, with clear negative result. 17. Has active substance abuse, including alcohol. 18. Has a known hypersensitivity or contraindication to procedural or post-procedural medications which cannot be adequately managed medically. 19. Has a known hypersensitivity to Neuspera's SNS System device components. 20. Has previously failed SNS therapy. 21. Has active implantable medical devices such as neurostimulators, drug pumps, pacemakers, or internal defibrillators since compatibility has not been assessed. 22. Has known needs for diathermy (shortwave, microwave, or therapeutic ultrasound) and radiofrequency ablation, in the vicinity of the neurostimulator since these procedures have not been evaluated. 23. Has a known need for therapeutic ultrasound in the area of the sacral nerve neurostimulator as the device can inadvertently concentrate the ultrasound field and cause harm. 24. Has a known need for therapeutic ionizing radiation as can damage the electrical components of the sacral nerve stimulator and any damage may not be immediately detectable. 25. Has plans to enroll or is currently enrolled in another investigational device or drug trial during his/her participation in this study. 26. The investigator is unable to elicit an appropriate motor response in the subject during the intra-operative testing of the implant procedure.
Statistical analysis	
Statistical design	The study will be conducted in two phases: In Phase I, the trial was designed to allow the enrollment of up to 55 subjects and to implant approximately 40 of these subjects to assess the utilization of the system during the SNS trial period and to help inform the length of hours of daily stimulation to be used in the second phase. A total of 34 subjects were implanted in Phase I.

	Phase II will enroll an independent group of up to 255 subjects resulting in 120 implant attempts, approximately 114 successful implants, to assess the safety and efficacy of the Neuspera SNS system at 6 months for the primary efficacy endpoint, and again at 6 and 12 months for safety and efficacy endpoints. The sponsor intends to file a PMA submission at the end of six-months of follow-up if the primary endpoint is achieved. Phase I analysis may occur at several points during the trial as the sponsor wishes to assess compliance and the performance of the system as this will be the first chronic use of the system. An interim analysis did occur at the completion of the 1-month post-trialing period of Phase I and again when the majority of subjects had completed 3 months of follow-up. The data from Phase I will not be the basis for formal conclusions; the intent was to gain initial data to inform the treatment for Phase II. Analysis of Phase II will occur when all subjects have completed 6 months post-implant (or are exited from the study). An interim analysis will be performed when the 60th Phase II subject has completed the 3-month post-implant visit. The study will be completed to the planned sample size of 120 attempted implants regardless of the outcome of the interim analysis. Revisions will not count towards attempted implants.
Analysis Populations	**Intent-to-Treat (ITT) Analysis Set**: The ITT analysis set is defined as all Phase II subjects who have signed informed consent. Demographic information and study exit details will be reported separately for those subjects included in the ITT population where no initial implant was attempted. **Modified Intent-to-Treat (mITT) Analysis Set:** The mITT analysis set is defined as all Phase II subjects for whom an initial implant is attempted. **Implanted Analysis Set**: The Implanted analysis set is defined as all Phase II subjects who are implanted with the Neuspera SNS system. **Responder Analysis Set:** The Responder analysis set is defined as subjects who are implanted with the system and are defined as responders at the Day 28 or Day 42 clinic visit post-implant. **Per Protocol (PP) Analysis Set:** The Per Protocol analysis set is defined as implanted subjects who have no protocol deviations that may significantly affect the primary endpoints. The determination of subjects excluded from the Per Protocol analysis set will be made prior to analysis.

Primary Safety Analysis	There is no planned statistical hypothesis test for the primary safety endpoint. The proportion of subjects experiencing an event, as well as the numerator and denominator, and the associated two-sided exact 95% binomial confidence interval will be provided. Values will be expressed as percentages. The primary analysis population for the primary safety endpoint is the mITT analysis set. Any adverse events reported for enrolled subjects who are excluded from the mITT analysis set, will be reported separately for the duration of participation in the study.
Primary Efficacy Analysis	Calculation of the primary efficacy endpoint will be based on the mITT analysis set. The statistical hypothesis test for the primary efficacy endpoint will be based on comparing the percentage of subjects with at least 50% improvement in UUI symptoms (therapy responders) to a null value of 50%, the same performance goal as in the study by McCrery et al.[6]. Mathematically, the null and alternative hypothesis are stated as: Ho: $p \leq 0.50$ Ha: $p > 0.50$ The null hypothesis will be rejected at the one-sided 0.025 alpha level based on a one-sided, one-sample exact tests of binomial proportions for responders. The proportion of 0.50 for responders corresponds to a value of 50%. Study success is defined as successful rejection of the null hypothesis. The 50% reduction in UUI symptoms treats subjects as their own control and is based on a clinically meaningful improvement at the subject level in the primary efficacy endpoint[4-6]. Successful rejection of the null hypothesis will indicate a clinically meaningful result in the majority of subjects by a statistically significant amount.
Additional Statistical Analysis	Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical variables will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and Clopper-Pearson Exact method for categorical variables.

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ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
AIMDD	Active Implantable Medical Devices Directive
ASADE	Anticipated Serious Adverse Device Effect
CIP	Clinical Investigation Protocol
CRF	Case Report Form
CRO	Contract Research Organization
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EDC	Electronic Data Capture
FI	Fecal Incontinence
eCRF	Electronic Case Report Forms
ePRO	Electronic Patient Reported Outcome
IB	Investigator Brochure
ICF	Informed Consent Form
IFU	Instructions for Use
ISO 14155	International Standard on the Clinical investigation of medical devices for human subjects – Good clinical practice
MedDRA	Medical Dictionary for Regulatory Affairs
MRI	Magnetic Resonance Imaging
NSM	Neuspera Medical
OAB	Overactive Bladder
PI	Principal Investigator
PGI-I	Patient Global Impression of Improvement
QA	Quality Assurance
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SNS/SaNS	Sacral Nerve Stimulation
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
UUF	Urinary Urgency Frequency
UUI	Urinary Urgency Incontinence
USADE	Unanticipated Serious Adverse Device Effect
WT	Wireless Transmitter

REVISION HISTORY

Version	Date	Summary of Changes/Affected Sections
1.0 (not approved or released)	06 March 2019	Initial for Regulatory Submission
2.0	21 May 2019	Response to FDA deficiencies
3.0 (not submitted in the US or released in Europe)	29 July 2019	Response to EC deficiencies and general updates throughout protocol and improving the flow of protocol.
4.0 (not approved or released)	25 September 2019	Made clarifications and added data collection parameters.
5.0	23 October 2019	Made change to section 10.3 regarding retention of informed consent.
6.0	05 December 2019	Clarified the timing of fecal incontinence (FI) diary. Change the OAB washout period. Added in data collection parameters for device testing and if subject requires MR scan. Changed volume of device. Made general updates to match Investigator Brochure version 4.0 updates.
7.0	28 January 2020	To increase the number of Phase I clinical sites from 6 to 9 sites in the US and Europe. Synopsis: Investigation Centers and Section 7.1.3: Study Sites and Subject Enrollment Limits
8.0	01 May 2020	To increase the number of Phase I clinical sites from 9 to 14 sites in the US and Europe. Synopsis: Investigation Centers and Section 7.1.3: Study Sites and Subject Enrollment Limits
9.0 (not approved or released)	20 May 2020	To remove three inclusion criteria (BMI requirement, Urodynamics and cystoscopy testing), to clarify the active implantable devices exclusion criterion, to add a baseline/screening assessment to measure the skin to S3 foramen distance, to allow final analysis of Phase I data on 1-month or 3-month follow-up data, and other administrative changes.

Version	Date	Summary of Changes/Affected Sections
10.0	17 July 2020	To reinsert inclusion criteria requiring urodynamics and cystoscopy testing within 6-months of the baseline/screening visit or completion of the tests at the screening baseline visit (these were removed in version 9.0 of the protocol). To add an inclusion criterion requiring that a subject's BMI be ≥ 18. To add an exclusion criterion that if, during the implant procedure, the investigator is unable to elicit an appropriate motor response in the subject during the intra-operative testing, the subject will be excluded.
11.0	06 October 2020	Updated the number of subjects to be enrolled in Phase I to up to 55 subjects to allow for up to 40 subjects to be implanted. Clarified definition of enrollment. Updated the formatting in Tables 4 and 6 to fit table on one page.
12.0	14 January 2021	Changed title to UUI population. Changed the definition of enrollment for Phase II to be consistent with ISO 14155. Updated number of enrolled subjects in Phase II to 255. Added an as treated analysis in Phase II, all implanted subjects will be followed. All subjects, regardless of responder or non-responder status at day 28 or 42 post implant will continue in post-implant follow-up. Changed post-implant visits to monthly though 12-month follow-up and every three months thereafter. Added monthly telephone visits mid-way between clinical visits through 12 months. Added post 12-month telephone visits in months where there is not a clinic visit. Changed anticipated length of follow-up to 36 months. Added a new device model, the size 44mm neurostimulator for use. Added procedures for device replacement. Added statement on limiting physical activity for 6 weeks post-implant. Added restrictions on device manipulation. Added troubleshooting procedures if subject not feeling stimulation. Added analysis plan for hierarchical testing of secondary endpoints intended for labeling claims. Added null and alternative hypotheses for secondary endpoints intended for

Version	Date	Summary of Changes/Affected Sections
		labeling claims. ISO14155-2020 compliance changes made in protocol.
13.0 (not approved or released)	16 March 2021	Changed the primary endpoint analysis population to an Intent-to-Treat Analysis Set. Added a Per Protocol Analyses set. Changed post implant visits to monthly through 6-months, quarterly to 12 months and then every 6-months thereafter. Added a physician review panel as a final check for trial qualification prior to implant attempt. Added another external stimulator model (low output) for intraoperative testing. A new undergarment and manufacturer have been added. New figures added with new undergarment. Added Charging Pads to the list of manufacturers for the components of the system. Removed the fecal incontinence (FI) diary for those subjects with concomitant FI at baseline. Justification for Clinician Investigation changed to include Phase I results. The model 000197 number was changed to SNS-35. Clavien-Dindo Classification System for Adverse Events replaced previous Adverse Event severity classification system. Other minor modifications throughout.
14.0 (not approved or released)	14 July 2021	Added a monitoring of safety events by the DSMB after every 36 subjects are implanted. Added inclusion criteria No. 13: Has appropriate sacral anatomy as determined by sponsor's and investigator's analysis of radiographic imaging. (The distance from the surface of the skin in the prone and seated position to the bone edge of the S3 foramen must be within the capabilities of the system). Added an assessment of sacral thickness to guide selection of implant model (SNS-28 or SNS-35) for the implant procedure. Added assessment of distance from the surface of the skin to the bone edge of the S3 Foramen in subjects with a BMI between 30 to 40 kg/m^2 or in subjects with a BMI<30 kg/m^2 based on investigator discretion. Update the follow-up visit windows for months 1 to 12 to be +/- 14 from Implant. Updated Figure 6 and 9 with new clinician application/patient application interface consistent with approved software. Updated protocol throughout with

Version	Date	Summary of Changes/Affected Sections
		more details associated with ISO 14155-2020 and EU MDR requirements/updates.
15 (not approved or released)	17 November 2021	Updated Figure 1 to include a picture of the Magnet. Added new section 2.19 with the Magnet description. Added new Figure 9 with a picture of the Magnet and updated Figure numbers throughout document. Added study stopping rules. Added rationale for stopping rules. Updated post-operative care section 7.1.5.7.3 regarding limiting delivery of therapy during certain activities such as driving. Updated adverse events section to be in compliance with new MDR regulations. Removed "Activities by Sponsor Representatives" section and combined information with section 12.2.1 Sponsor Representatives. Updated section 4.4 to include a separate table of device and procedure related adverse events from Phase I of the trial. Updated table on potential risks. Added primary and secondary mitigators for device fracture and dislodgement. In section 8.4.2 added new adverse event reporting timeframes for fractures, dislodgements/migrations and surgical revisions. Adverse event causality relationship definitions were updated. Administrative changes throughout.
16	08 March 2022	Updated Phase II stopping rules for continual monitoring of device fracture, dislodgement/migration, and surgical revisions. Updated actions taken if a stopping rule is met. Changed reporting time of Sponsor to the FDA on lead migration/dislodgment, fracture, and loss of therapy to the DSMB and FDA from 15 days to 10 days. Added that accounting of all device events or malfunctions (i.e. migrations/dislodgements and fractures), whether clinically significant (requiring revision or resulting in permanent loss of therapy) or not, with a further breakdown of how they are dealt with (e.g., no action needed, reprogramming, permanent loss of therapy and/or surgical revision/explantation) will be completed. Changed the coordinating investigator from Dr Steven Siegel to Dr Osvaldo Padron. Requirement of recording in the

Version	Date	Summary of Changes/Affected Sections
		stimulation diary changed to recording therapy sessions daily, ≤ Month 12 Visit, and weekly, > Month 12 Visit in Phase I and Phase II. Change statistical section presentation of secondary endpoints to match synopsis; endpoints themselves did not change. Added the contact information for the new CROs, NAMSA and Axiom. Added a new Figure 1.
17	26 April 2022	Updated to indicate that an interim analysis will be completed when approximately 50% of subjects complete the 3-month follow-up visit. Updated undergarment wording to indicate low-rise hipster will be provided to female subjects who are allergic to natural rubber. Clarified the material in the two versions of female low-rise hipster. Described the encasement of natural rubber in the undergarments. Added in time points in which measurements will be taken for undergarment. Added a sample subject identification card provided to subjects. Added that in the event of early termination or at the completion of the investigation that the sponsor will notify the FDA, IRBs and investigations within 30 days. Additionally, a final report will be submitted to the FDA, IRBs and investigators within 6 months of termination or completion of the investigation. Added Other Serious (Important Medical Events) to the adverse event section. Added statement that Phase I data in the 65 and older population is reflective of the Phase I group as a whole. Remove subject pain questionnaire.
17.1	23 February 2023	Added Canada as geographical location for an additional clinical site.
18	05 April 2023	The enrollment period for Phase II was extended from 9 to 12 months. The number of scheduled telephone visits in Phase II was decreased. Updated number of explants and safety data. Increased estimated time of Phase I subject involvement. Removed requirement for undergarment measurement and weight. Changed exclusion criteria for UTI. Added definition of mITT and changed definition of ITT analysis set. Modified activity

Version	Date	Summary of Changes/Affected Sections
		restrictions post implant. Updated Figure 10, Patient Controller running the Neuspera Application software. Stimulation sensation verification was changed to complete at the end of the therapy session instead of during the therapy session. The person(s) who may perform the Sacral Anatomy reading was updated. Scheduled device parameter/downloads was revised to be periodically recorded. Added information on what should not be considered an AE. Updated quantitative endpoints for OAB.
19	12 June 2023	Increased number of clinical sites from 25 to 35. Lowered the number of attempted implants from 145 to 120. Lowered the approximate number of successful implants from 138 to 114. Lower the power for a one-sided 0.025 exact binomial test from 90 to 85%. Updated the "worst case" scenario results that would still meet the statistical threshold for this performance goal, changed to 72 out of 120 (60%). Added a ICIQ-OABqol responder rate secondary endpoint to be potentially used for labeling claims. Added statistical information per FDA feedback. Updated details on interim analysis.
20	16 March 2024	Updated safety information based on 2023 FDA annual report. Incorporated Neuspera Wearable into the study. Refined secondary endpoints that will be included for labeling claims. Removed the 12-month time point assessment for all secondary endpoints that may be used for labeling claims. Noted that performance goals for all secondary endpoints are included in the Statistical Analysis Plan (SAP). Added that subjects who take OAB medications prior to the six-month visit will be considered device failures. Added Phase II weight assessment at 12, 24, and 36 month visits (and 42 and 60 month visits for Phase I subjects). Added bladder diary assessments to every clinical visit in Table 8. Added that a delegated implanting sub-investigator can complete the Physician User Experience Questionnaire. Noted that stimulation settings were recorded, but not downloaded. Noted that if a subject is symptomatic

Version	Date	Summary of Changes/Affected Sections
		with a urinary tract infection (UTI) prior to beginning or in the middle of a 72-hour bladder diary, it is recommended to the subject start the diary after the subject is asymptomatic after standard-of-care treatment. Updated Statistician to Fortrea. Formatting changes.
21	4 April 2025	Removed the specific brand name (Apple) reference on the Clinician Programmer and Patient Controller and described Neuspera Application software with off-the-self equipment. Added new Patient Controller picture. Updated Table 1 (Neuspera SNS System Manufacturers), the Neuspera App for the Clinician Programmer and Patient Controller added. Removed duplicate sciatica reference in Table 2 (Potential Risks Based on Literature Review and Neuspera Clinical Data). Updated Figure 17 (Troubleshooting guidance for loss of efficacy or painful stimulation) to include Wearable. Added a sub-study available for Phase I subjects only in Appendix A: Phase I Sub-Study

CONTACT INFORMATION

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1. INTRODUCTION

Millions of patients worldwide are diagnosed annually with overactive bladder (OAB) including urinary urgency, frequency, nocturia and urinary urgency incontinence (UUI). An estimated 546 million patients will be affected by OAB of which 423 million patients will be affected by UI.[1] Many in this patient population are not well controlled by conventional medical management.

The International Continence Society (ICS) defines UUI as a "Complaint of involuntary loss of urine associated with urgency." Patients with UUI often experience urinary urgency at inconvenient or unpredictable times and often experience leakage and voiding in advance of reaching a toilet. As a result, these symptoms interfere with normal daily activities such as work, intimacy, and sexual function. This disruption to the patient's normal daily activity leads to embarrassment, depression, diminished self-esteem, and reduced quality of life.[2]

The clinical diagnosis of OAB is based on a history and physical examination of the patient, as well as urinalysis. In some patients, additional procedures and measures may be necessary to validate an OAB diagnosis or exclude other disorders. A urine culture and/or post-void residual assessment may be performed and details from bladder diaries and/or symptom questionnaires may be obtained.

1.1 Treatment of Overactive Bladder

Multiple options are available to patients who are diagnosed with overactive bladder (OAB). Physicians typically take a guideline-based phased approach to the treatment of symptoms with OAB.[3]

1.1.1 First-Line Treatment

First-line treatment for UUI as a consequence of OAB includes behavioral therapies such as bladder training, bladder control strategies, pelvic floor exercise, and fluid management. Behavior therapies may be combined with pharmacologic management.

1.1.2 Second-Line Treatment

When symptoms are not adequately improved with first-line treatment, second-line treatment includes oral anti-muscarinics, and β_3-adrenoceptor agonists. If a patient continues to experience inadequate symptom control and/or unacceptable adverse events with one anti-muscarinic medication, then a dose modification or different choice of anti-muscarinic or β_3-adrenoceptor agonists may be tried.

1.1.3 Third-Line Treatment

Third-line treatments include neuromodulation and bladder chemo denervation with Onabotulinumtoxin A injection. These third-line options bridge the treatment gap between conservative therapies for UUI as a consequence of OAB and irreversible surgical procedures such as enterocystoplasty.

Neuromodulation targets the sacral nerve plexus which regulates control of the bladder and pelvic floor muscles. Neuromodulation treatments currently available for OAB are Sacral Nerve Stimulation (SNS) and Posterior Percutaneous Tibial Nerve Stimulation (PTNS).

For SNS therapy, two systems are commercially approved: Medtronic InterStim and Axonics Neuromodulation System. The Medtronic InterStim® Therapy and Axonics systems are indicated for the treatment of urinary retention and the symptoms of OAB, including UUI and significant symptoms of urgency-frequency, alone or in combination in patients who have failed or could not tolerate more conservative treatments. Sacral Nerve Stimulation using the InterStim® Therapy system has been shown in an as treated analysis to have a therapeutic success of 76% (93% were female) versus 49% for standard medical therapy (P = 0.002).[4] Device related complications associated with the InterStim® Therapy system include the following: lead migration and fracture, pocket infection, lead infection, pocket pain, cosmetic issues including a bulge above the buttocks and requirement for frequent reprogramming. Device related adverse events occurred in 31% of patients with InterStim system versus 27% of adverse events in patients with standard medical therapy. A 5-year prospective, multicenter, non-randomized study of 272 subjects implanted with InterStim for treatment of OAB demonstrated successful long-term outcomes using sacral neuromodulation. The InSite Study showed that of the 272 subjects with OAB there was a therapeutic success rate of 67% (95% CI 60-74) using a modified completers analysis and 82% (95% CI 76-88) using a completers analysis.[5]

The Axonics system, in an as treated analysis, at 6 months, showed a therapeutic success rate of 90% (116/129 subjects). The average number of UUI episodes was reduced from 5.6 ± 0.3 at baseline to 1.3 ± 0.2 at 6 months ($p<0.0001$) representing a 79% reduction in UUI episodes. The most frequent adverse events (AEs) were discomfort due to stimulation, pain at the neurostimulator site, and lead migration.[6] The 1-year, as treated, outcomes data demonstrated that 89% of study participants (115/129) were therapy responders (i.e., had ≥50% reduction in UUI symptoms as compared to baseline). A consistent responder rate was seen from 1-month to 1-year. The UUI episodes reduced from 5.6 ± 0.3 at baseline to 1.4 ± 0.2 at 1-year ($p <0.0001$) which is a 75% reduction in UUI episodes. The most frequent AEs were discomfort due to stimulation, discomfort/heating near the charging area, pain at the neurostimulator site, and lead revision.[7]

2 INVESTIGATIONAL DEVICE

2.1 Neuspera Implantable Sacral Nerve Stimulation System

The Neuspera Implantable Sacral Nerve Stimulation System (herein referred to as **Neuspera SNS system**) is a sacral nerve stimulation system consisting of a miniaturized implantable neurostimulator system combining a receiver antenna, hermetically sealed electronic package, and tined stimulation electrode array with four programmable electrodes. The neurostimulator's antenna receives energy from an externally worn powering unit (Wireless Transmitter, see below). The hermetically sealed electronic package (0.03 cc) consists of a highly integrated electronic circuit with a custom ASIC (application specific integrated circuit) and flex circuit interconnect. This package harvests the received energy, manages power and communication, and generates stimulation, analogous to the InterStim® implantable pulse generator (IPG). The programmable electrode array is similar in geometry and functionality to the electrode array at the distal end of the InterStim lead. The electrode array delivers stimulation to the sacral nerve.

The Neuspera SNS system is provided in two sizes: 44 mm length (Model SNS-28) and 51 mm length (Model SNS-35).

There is no implantable battery in the Neuspera SNS system. The absence of the implantable battery and the miniaturized electronic package reduces the total implanted volume of the Neuspera SNS system to approximately 0.12 cc. As noted above, the volume of the Neuspera pulse generator (hermetically sealed electronic package) is 0.03 cc vs the InterStim II implantable pulse generator volume of approximately 14 cc or the InterStim Micro implantable pulse generator volume of approximately 2.8 cc. The Neuspera SNS system is powered by an externally worn Wireless Transmitter which contains a rechargeable battery. Power is delivered to the implanted neurostimulator using Neuspera's proprietary mid-field powering technology. The Wireless Transmitter is worn over the subject's sacrum, directly over the implanted neurostimulator, and held in position by custom designed undergarments or Wearable. The Wireless Transmitter is controlled by custom Neuspera software Application (referred to as the Clinician Programmer and the Patient Controller) running on off-the-shelf equipment. The rechargeable battery of the Wireless Transmitter is charged by an off-the-shelf charging pad.

The tools provided in the Neuspera Implantable SNS Kit are used to introduce and implant the neurostimulator. Additionally, the Neuspera Intraoperative Test Kit and an off-the-shelf Intraoperative External Stimulator are used to identify the location of the sacral nerve by observing motor responses (bellows response and great toe/toe flexion) to stimulation.

The Neuspera Implantable SNS System consists of:

- Implantable Sacral Nerve Stimulation Kit
    - Foramen Needle and Stylet Set
    - Guidewire
    - Dilator/Introducer Sheath Set
    - Implant/Push Rod Assembly
- Intraoperative External Stimulator

- Intraoperative Test Kit
    - Intraoperative Stimulator Lead (cable)
    - Alligator Clip
    - Surface Electrode
- Wireless Transmitter
- Magnet
- Neuspera Undergarments
- Neuspera Wearable
- Clinician Programmer
- Patient Controller
- Wireless Transmitter Charging Pad

Figure 1 displays the Neuspera SNS System. A detailed description of each relevant component is provided in the sections that follow.

The following components will have contact with subject tissue or bodily fluids:

- Implantable Sacral Nerve Stimulation Kit
    - Foramen Needle and Stylet Set
    - Guidewire
    - Dilator/Introducer Sheath Set
    - Implant/Push Rod Assembly
- Intraoperative Test Kit
    - Surface Electrode (short-term skin contact only)
- Neuspera Undergarments (skin contact only)
- Neuspera Wearable (skin contact only)

Additionally, the following components are intended to be handled (held and/or touched) by subjects:

- Wireless Transmitter
- Magnet
- Patient Controller
- Wireless Transmitter Charging Pad
- Neuspera Undergarments
- Neuspera Wearable

Figure 1: Neuspera Implantable SNS system

2.1.1 Principle of Operation

Neuspera's SNS System relies on a radio frequency signal that is sent from the Wireless Transmitter to power a miniature neurostimulator implanted in the S3 Foramen in close proximity to the sacral nerve.

The Neuspera's SNS System uses a midfield radio frequency (RF) signal within the FCC ISM (industrial, scientific, and medical) radio band between 902 and 928 MHz as the default band. The RFID (radiofrequency identification) band between 865 and 868 MHz is available as an alternate band in regions where the ISM band cannot be used. The neurostimulator has an antenna at its proximal end that receives the signal. The received signal passes from the antenna through the proximal bipolar

feedthrough to the circuit assembly within the sealed circuitry housing. The controller integrated circuit (IC) with circuit assembly rectifies the antenna signal and uses the harvested energy to power the internal implant circuitry. The incident signal is also modulated by the wireless transmitter to encode information that is used by the implant to set parameters of the therapeutic pulse output. The pulses are conducted through the distal quadripolar feedthrough to the distal electrodes used for stimulation of the subject's sacral nerve.

This midfield powering technique efficiently couples the RF signal through the subject's tissue to the implanted device. The dielectric properties of the tissue between Wireless Transmitter and the Implantable Neurostimulator are factored into the transmitter design and transmission frequency. This enables a much higher energy transfer efficiency relative to comparable near field or far field-based implantable device systems. In the simulation generated field density plot, the Neuspera Medical radio frequency (RF) Mid-Field signal emanating from the Wireless Transmitter (top in Figure 2) is shown propagating through the subject's tissue to the Implantable Neurostimulator (bottom in Figure 2). The energy from this RF field is received in the antenna at the proximal end of the Implantable Neurostimulator. Circuitry within the sealed circuit assembly decodes telemetry data, rectifies energy from the field, and generates programmed neural stimulation pulses at the distal end of the device when instructed by the Wireless Transmitter.

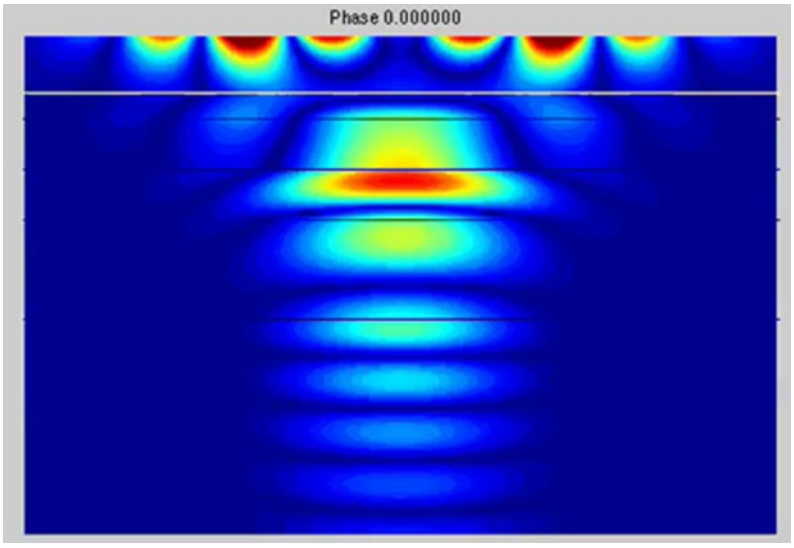


FIGURE 2: NEUSPERA'S RF MID-FIELD FROM THE WIRELESS TRANSMITTER THRU THE SUBJECT TISSUE TO THE IMPLANTABLE STIMULATOR

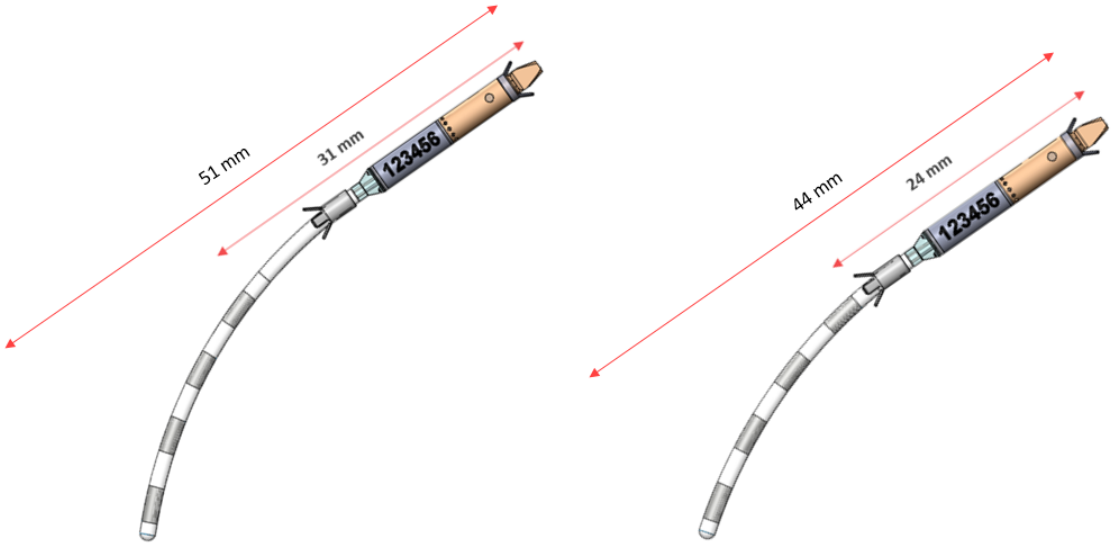
2.1.2 Implantable Neurostimulator

The sterile Implantable Neurostimulator (neurostimulator) is constructed of commonly used materials and available in two lengths measuring approximately 51 mm long and 44 mm long and 2.3 mm in diameter at its widest point. Figure 3 shows the device differences in device length from the proximal end to the first electrode for the two implant models. The distal portion of the implant is pre-formed with a curvature intended to mimic to the physiologic curvature of the sacral nerve sheath; an incorporated keying feature mates with the Push Rod to prevent accidental rotation of the pre-formed curve during the implant procedure.

The tined neurostimulator electrode has an internal circuit assembly that is connected, welded, and sealed within a housing. On its distal end, it has four 3mm electrodes, spaced at 3mm intervals that create a bipolar stimulation field. On the proximal end, it has an encapsulated antenna to receive the propagated midfield signal from the Wireless Transmitter; the implant does not contain a battery. The radial tines maintain the axial position of the implant. The suture on the proximal end of the implant (not shown) is designed to remain tethered to the stimulator during the trial period to simplify removal of the device in the event of an unsuccessful trial period. Due to the duration of the trialing period in the clinical trial, the suture is trimmed and tucked under the skin at the time of implant.

One implantable neurostimulator will be implanted per subject. Subjects receiving the Neuspera SNS System will have the system in place for the duration of their participation in the study. After study completion, subjects may choose to leave the system in place.

Please refer to Neuspera's Implantable Sacral Nerve Stimulator Kit Instructions for Use.



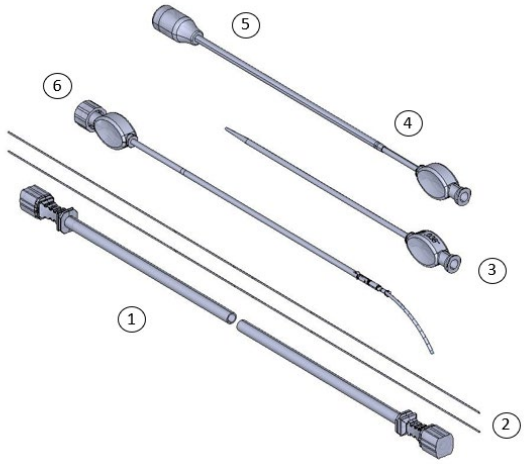
Model: SNS-35
Longer Implant
Volume: 0.12 cc

Model: SNS-28
Shorter Implant
Volume: 0.11 cc

FIGURE 3: NEUSPERA SNS IMPLANTABLE NEUROSTIMULATORS

2.1.3 Implantable Sacral Nerve Stimulation Kit

The Implantable Sacral Nerve Stimulation Kit contains the Implantable Stimulator (described above) pre-loaded on the Push Rod (Implant/Push Rod Assembly) in addition to tools needed to introduce and implant the neurostimulator. The Implantable Sacral Nerve Stimulation Kit is shown in Figure 4.



1. Foramen Needle and Stylet Sets (shown with protective cover; n=2)
2. Guidewires (n=2)
3. Pre-dilator
4. 7F Dilator
5. Introducer Sheath
6. Implant/Push Rod Assembly

FIGURE 4: IMPLANTABLE SACRAL NERVE STIMULATION KIT COMPONENTS

The Implantable SNS Kit contains:

- Foramen Needle and Stylet Sets (n=2)
- Guidewire (n=2)
- Dilator/Introducer Sheath Sets
    - Pre-dilator
    - 7F Dilator
- Implant/Push Rod Assembly

Each item noted above is described in the remainder of this section.

Foramen Needle and Stylet: The sterile, custom stainless steel 20-gauge foramen needle (with stylet) is inserted under fluoroscopy into the S3 foramen, and the needle is used with the components of the Intraoperative Test Kit (i.e., electrical clips, cable, and surface electrode) and the Intraoperative External test stimulator to conduct an initial assessment of the subject to determine their responsiveness to stimulation therapy prior to implanting the neurostimulator.

Guidewire: The guidewire is a 0.6 mm diameter stainless steel wire measuring 305 mm long to place the Pre-dilator and 7F Dilator/Introducer Sheath Assembly. During the implant procedure, the guidewire is placed through the lumen of the foramen needle. The foramen needle is then removed.

Dilator/Introducer Sheath Set: Custom dilators and an introducer sheath are used to introduce the Implant/Push Rod Assembly to the implant location. The Pre-Dilator is inserted over the guidewire and then removed, keeping the guidewire in place. The 7F Dilator/Introducer Sheath Assembly is then inserted over the guidewire. Once the 7F Dilator/Introducer Sheath Assembly is in place, the guidewire

and then the 7F Dilator are removed. The Pre-Dilator and 7F Dilator each have a distal radiopaque marker.

Implant/Push Rod Assembly: The Implantable Neurostimulator is supplied pre-loaded on a Push Rod to form the Implant/Push Rod Assembly. The Assembly is inserted through the introducer sheath to properly place the neurostimulator in the correct implant location. Once the neurostimulator is in the correct position, the push rod is detached from the neurostimulator and removed.

2.1.4 Intraoperative Test Kit

The single-use Intraoperative Test Kit is used in conjunction with the Intraoperative External Stimulator and the Implantable SNS Kit to aid in finding the correct implant site for the Implantable Neurostimulator. The following accessories are packaged in the Intraoperative Stimulator Test Kit:

- Stimulator Lead (cable)
- Alligator Clip
- Surface Electrode (Ground pad)

The Intraoperative Test Kit components are commercially available products and are packaged and labeled by Neuspera Medical.

2.1.5 Intraoperative External Stimulator

The Intraoperative External Stimulator is used with the foramen needle and the Intraoperative Stimulator Test Kit to identify the location of the sacral nerve by observing motor responses (bellows response and great toe/toe flexion) to stimulation using the foramen needle. This is done to identify the best implant location for the neurostimulator.

As part of the clinical study, participating centers will be provided with the BioStim M7 Digital TENS unit from Biomedical Life Sciences, shown below in Figure 5. An additional low output BioStim model will be added for use in Phase II of the clinical trial.

FIGURE 5: BIOSTIM M7 DIGITAL TENS UNIT

2.1.6 Clinician Programmer

The Clinician Programmer (Programmer) enables management of the Wireless Transmitter associated with the subject's implant, programming a subject's stimulation therapy, review of subject's therapy statistics, and connection of a Patient Controller to a Wireless Transmitter. The Clinician Programmer runs Neuspera's software Application ("Neuspera App") on off-the-shelf equipment. Software updates may be provided throughout the study when approved for use by the FDA, Health Canada and the European regulatory authorities.

Clinicians will primarily navigate among four views on the programmer software application: Home Screen; Patient Information and Settings; Wireless Transmitter Management; and Therapy Configuration (Figure 6).

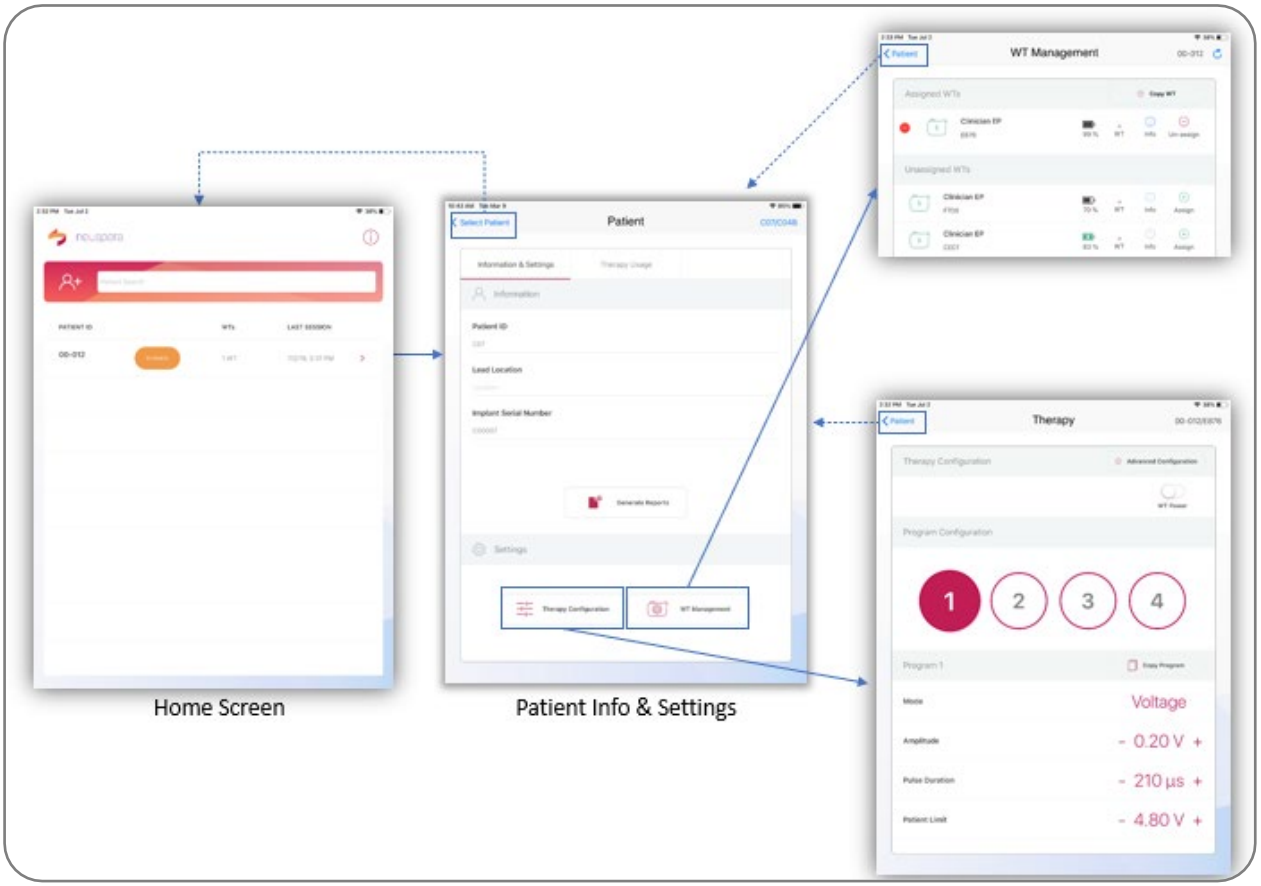


FIGURE 6: CLINICIAN PROGRAMMER INTERFACE

2.1.7 Wireless Transmitter

The Wireless Transmitter measures approximately 8 cm in diameter and is approximately 1.5 cm in thickness with a weight of 103g (Figure 7). The Wireless Transmitter can be turned on/off using the Patient Controller and Clinician Programmer and is designed to last 2 hours before recharging is

required. Depending on the prescribed stimulation session, multiple Wireless Transmitters may be provided to each subject to allow therapy delivery using one Wireless Transmitter while charging another Wireless Transmitter.

The Wireless Transmitter is placed in the pocket of the undergarment or Wearable (discussed below), which positions the Wireless Transmitter directly above the implanted neurostimulator. The Wireless Transmitter must be worn in the provided undergarment or Wearable.

The Wireless Transmitter contains an implant antenna and a programming antenna. The implant antenna transmits power and communicates with the implanted neurostimulator. The battery charging antenna recharges the Wireless Transmitter using common Qi charging. Additionally, there is a Bluetooth® antenna mounted on the printed circuit board (PCB) to communicate with the Clinician Programmer and the Patient Controller, allowing the user to adjust settings and activate or cease therapy. The internal components in the Wireless Transmitter are constructed of conventional surface mount electronics components and conventional circuit board substrate materials. The white outer shell is polycarbonate.

The Wireless Transmitter is water resistant and able to withstand daily cleaning. The Wireless Transmitter is internally powered (with a lithium-ion battery) and wirelessly recharged. The Wireless Transmitter can switch its operating frequency for international traveling.

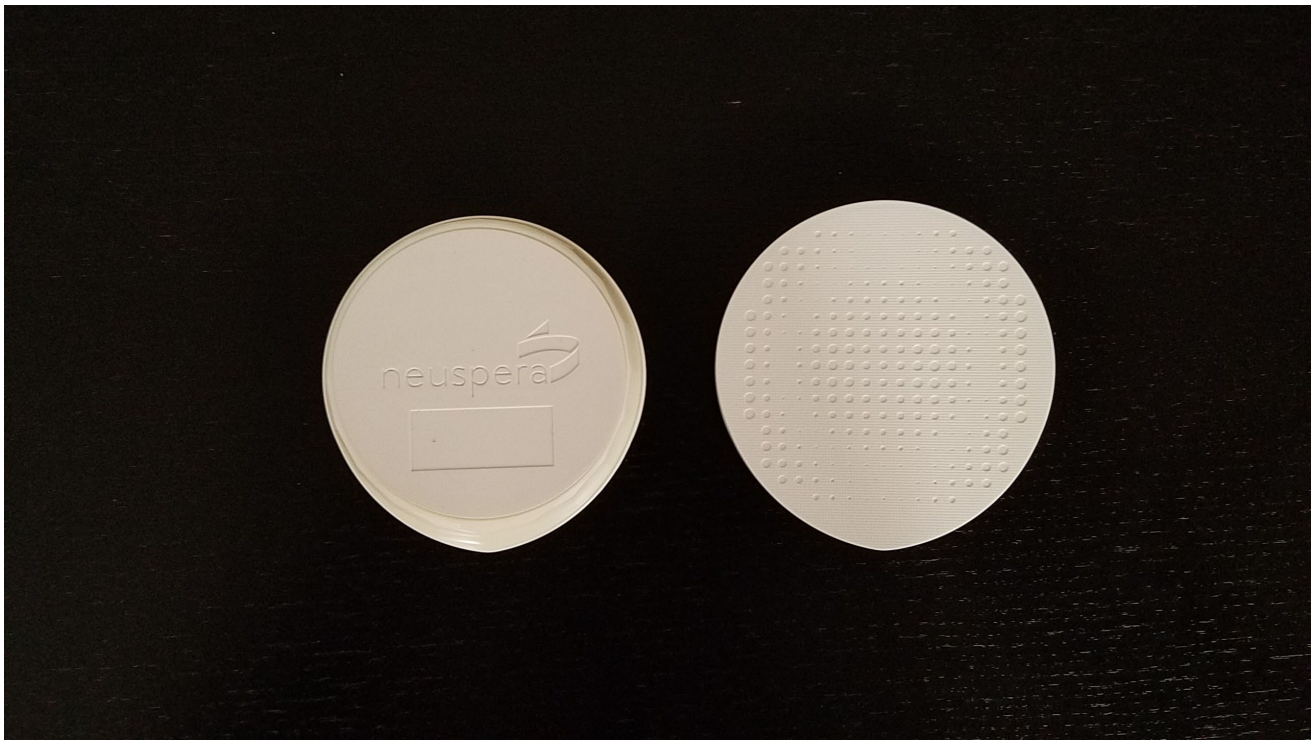


FIGURE 7: WIRELESS TRANSMITTER

2.1.8 Wireless Transmitter Charging Pad

The Wireless Transmitter charging pad shown in Figure 8 below is an off-the-shelf wireless charging pad which can be plugged into a wall or USB outlet. The Wireless Transmitter is placed white side facing up and the logo/label side facing down (i.e. device is “upside-down”) on the charging pad to charge (Figure 8). A light can be seen on the charging pad when the Wireless Transmitter is charging.

FIGURE 8: PHOTOGRAPH OF THE WIRELESS TRANSMITTER CHARGING PAD

2.1.9 Magnet

The Wireless Transmitter will be provided with a Magnet (Figure 9). The Magnet may be used to reset the Wireless Transmitter when the Wireless Transmitter is not charging appropriately or becomes inoperative. When the Wireless Transmitter needs to be reset, the subject will place the Wireless Transmitter correctly on the charging pad (dotted side face up as in Figure 8). The label side of the Magnet (bottom of Magnet) is placed against the dotted side of the Wireless Transmitter to perform the reset. The teardrop point of the Magnet should be aligned with the teardrop point of the Wireless Transmitter. After 5-10 seconds, remove Magnet from the Wireless Transmitter. The subject will confirm the reset was successful by 1) confirming the green light on the Wireless Transmitter is blinking and 2) waiting 30 seconds and observing that the status light of the charging pad has initiated. The magnet should not be left on the Wireless Transmitter when it is being charged between therapy sessions.

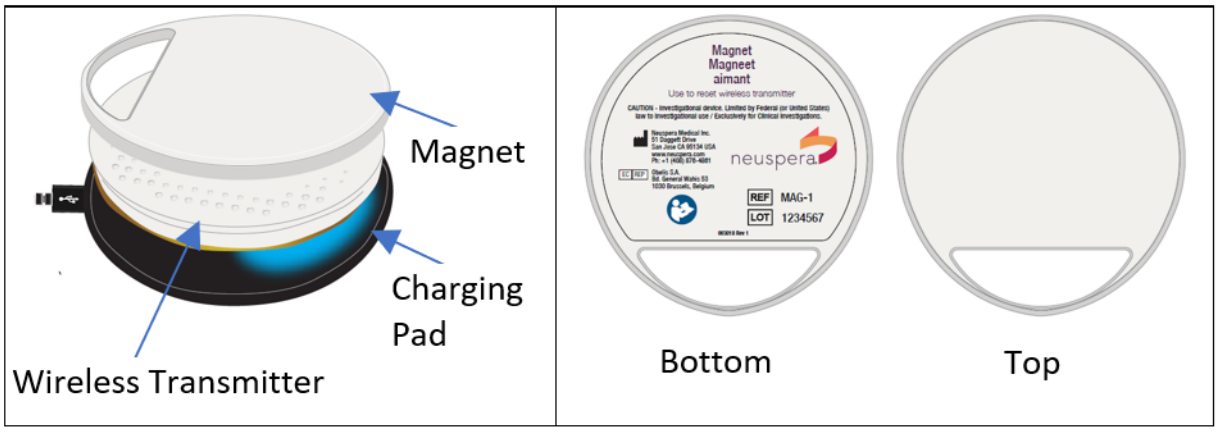


FIGURE 9:MAGNET

2.1.10 Patient Controller

The Patient Controller (Figure 10) runs Neuspera's software Application on off-the-shelf equipment. The Patient Controller comes with its own USB charging cord. The Patient Controller is used by the subject to turn their Wireless Transmitter on/off, adjust stimulation amplitude (within limits set by the physician) and select which of the physician's pre-programmed stimulation programs to use. The user can also monitor the Wireless Transmitter battery level, view his/her program use history and adjust the Wireless Transmitter for airplane and international travel.

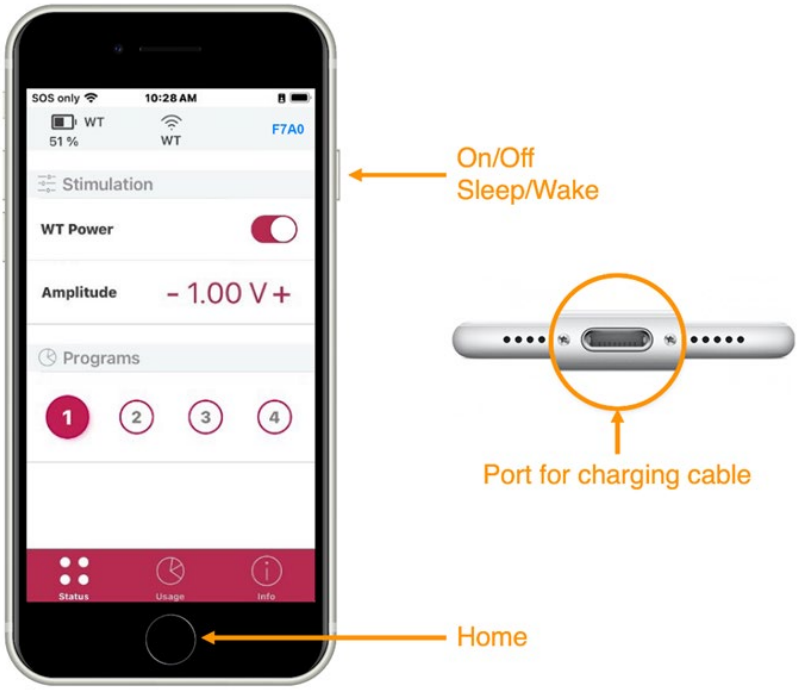


FIGURE 10: PATIENT CONTROLLER RUNNING THE NEUSPERA APPLICATION

2.1.11 Custom Undergarment

The custom designed Neuspera Undergarment is a pair of underwear with a rear pocket that comfortably positions the Wireless Transmitter in the correct position directly over the sacrum; see Figure 11 and Figure 12. The specially designed pocket in the undergarment includes a layer of foam to pad and insulate the Wireless Transmitter against the body to improve comfort and provide the optimal distance from the skin. During use, the Wireless Transmitter is inserted into the pocket such that the white (dotted) side faces the body, and the logo/label rim faces away from the body. The undergarment may be worn by itself or over pads or diaper. The custom undergarments are provided by two different manufacturers (see section 2.4). The pictures of the women's designs for both manufactures are provided in Figure 11 (Women's Panty) and Figure 12 (Women's Low Rise Hipster). There is also a Men's Brief that will be used for male subjects (as pictured in Figure 1 with the full system). The Men's Brief has the same rear pocket design as the Women's Panty design.

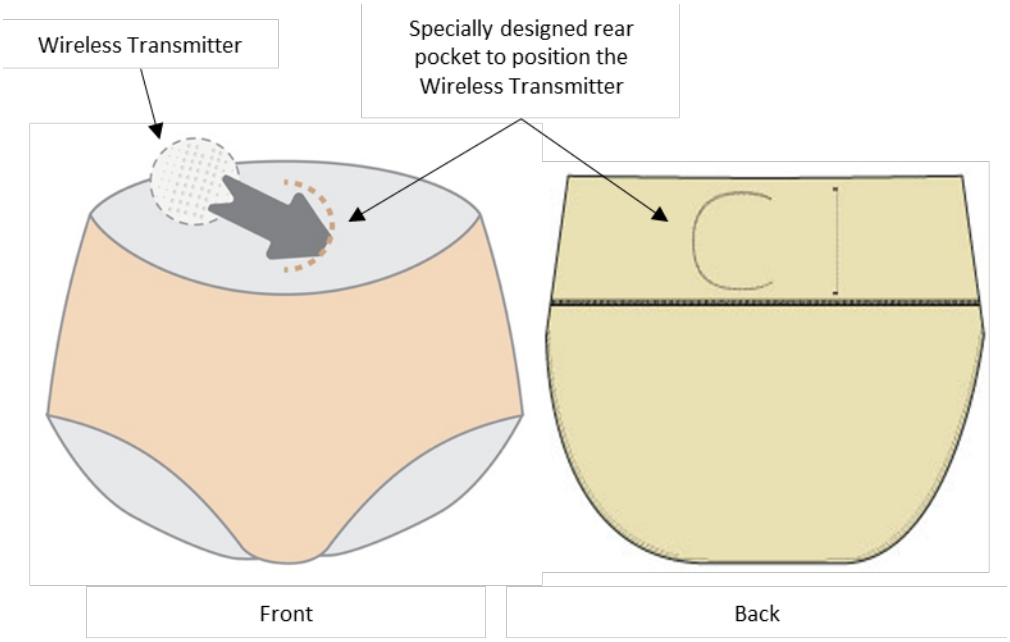


FIGURE 11: WOMEN'S PANTY UNDERGARMENT

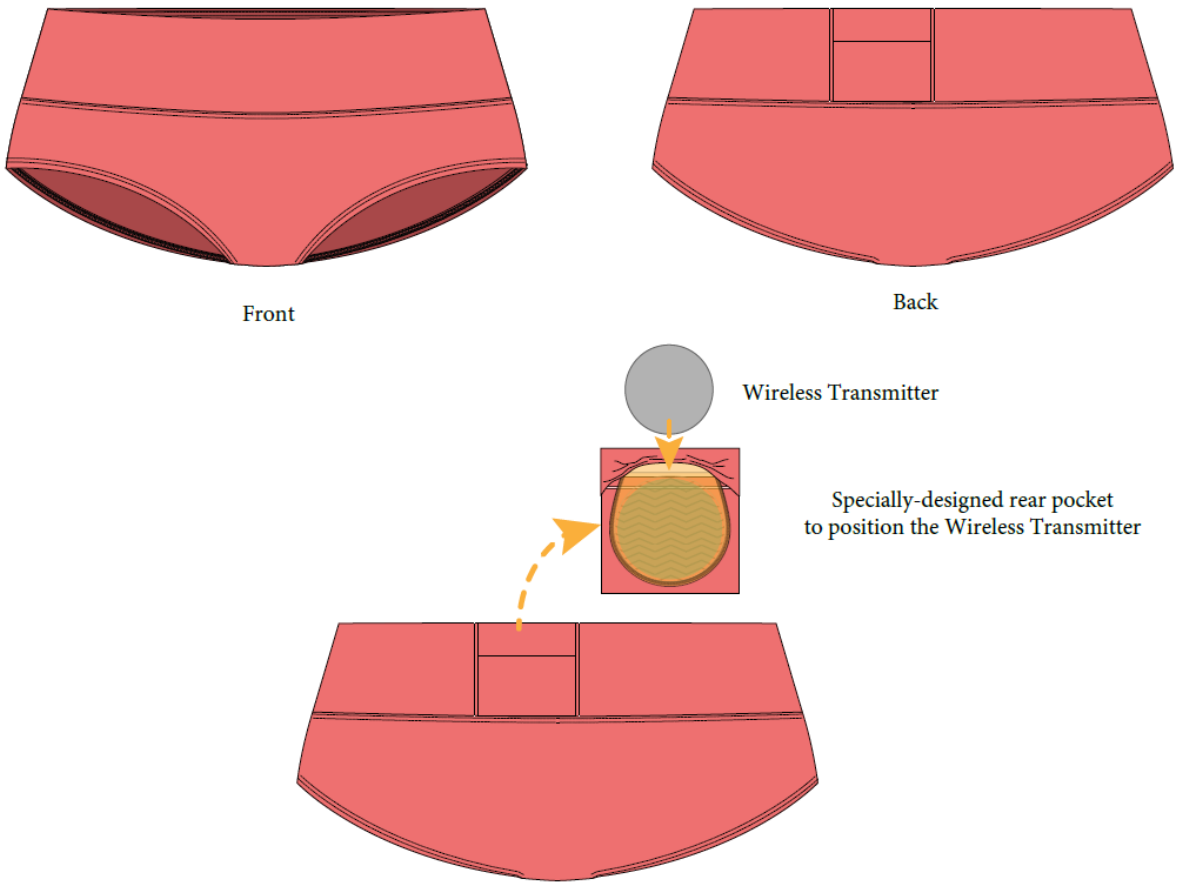


FIGURE 12: WOMEN'S LOW RISE HIPSTER UNDERGARMENT WITH REAR POCKET FOR THE WIRELESS TRANSMITTER

The undergarments are available with the pocket on either the right or left side, corresponding to the side in which the neurostimulator is implanted and come in men's and women's sized extra-small (XS) to extra-extra-extra-large (XXXL). The undergarments are made from standard garment material. The Women's Panty contains: spandex, nylon, polyester, cotton, and polyurethane. The Men's brief contains: spandex, nylon, polyester, cotton, natural rubber and polyurethane. The Women's Low Rise Hipster is provided in two versions that differ in materials only. One version contains: spandex, nylon, polyester, cotton, natural rubber, and polyurethane, and one version contains: spandex, nylon, polyester, cotton and polyurethane. All undergarment versions are worn the same way as standard undergarments.

All female subjects initially implanted in Phase II will be provided with Women's Low Rise Hipster garments containing natural rubber. Those subjects allergic to the natural rubber will be provided with the Low Rise hipster that does not contain natural rubber. All male subjects will receive the Men's brief containing natural rubber. Male subjects allergic to the natural rubber should discuss study participation with the clinical investigator. In the Women's Low Rise Hipster and Men's briefs containing natural rubber, the natural rubber is encased in two layers of polyester (Women's Low Rise Hipster) and polyester and cotton (Men's Brief). The two layers prevent the natural rubber from having direct skin contact. The first layer is within the elastic trim itself where the trim is made of natural rubber tubes wrapped in polyester. This elastic trim is incorporated into the waistband of the women's low rise hipster

garment where the main fabric (polyester/spandex) is wrapped around the elastic trim. In the Men's Brief, the elastic trim is incorporated into the leg opening of the men's brief undergarment where the main fabric (cotton/spandex) is wrapped around the elastic trim. Two layers of polyester between the skin (women's undergarment) and polyester/cotton (men's undergarment) and the natural rubber serves as a protective layer. The natural rubber is not intended to contact the skin and is unlikely to contact the skin of the subject during use; however, the undergarment will be labeled "Caution: This Product Contains Natural Rubber Latex Which May Cause Allergic Reactions." This information will be provided in the Subject Informed Consent, Patient Manual and Clinician Manual for the clinical trial.

2.1.12 Wearable

The Neuspera Wearable (Wearable) is designed to hold and maintain the Wireless Transmitter (WT) above the implanted neurostimulator for delivery of therapy. The specially designed pocket will also pad and insulate the Wireless Transmitter against the body to improve comfort. An optional leg loop strap is provided to offer additional support for maintaining vertical positioning. The Wearable is intended to be worn under general clothing (i.e. pants, shirts, and jackets) and over undergarments. It is also compatible with pads and diapers. The Wearable is available in four sizes from Small to Extra Large.

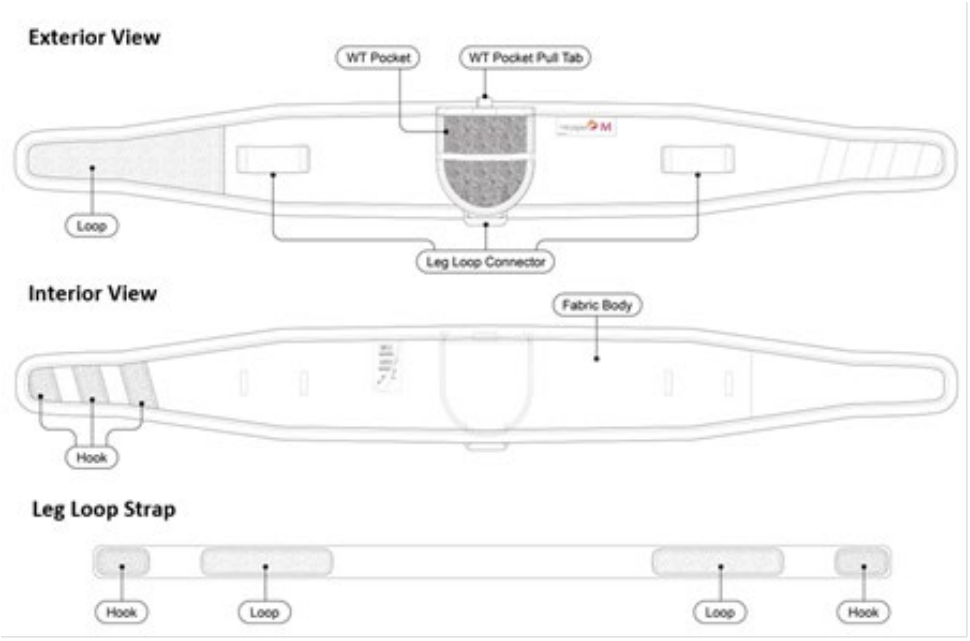


FIGURE 13: WEARABLE

2.2 Intended Use and Indications Statement

2.2.1 Intended Use

The Neuspera Implantable Sacral Nerve Stimulation System is intended for stimulation of the sacral nerve to treat urinary urgency incontinence (UUI) symptoms.

2.2.2 Indications Statement

Neuspera's Implantable SNS System is indicated to treat subjects with UUI who have failed or could not tolerate more conservative treatments.

2.3 Intended Purpose in the Clinical Investigation

The Neuspera’s Implantable SNS System is intended for stimulation of the sacral nerve to treat UUI symptoms. This study will collect data on the efficacy and safety of the Neuspera SNS system in subjects who have UUI.

2.4 Manufacturer

The Neuspera SNS System is a combination of a number of different devices. The devices of the Neuspera SNS system are manufactured at a mix of in-house and off-site contract manufacturers within the United States. Neuspera executes quality agreements and relies on supplier quality systems for adequate controls of documentation records.

Neuspera is the manufacturer of record / legal manufacturer and maintains control over all product released for clinical use.

The Table 1 below identifies the manufacturing facilities associated with the Neuspera SNS System:

TABLE 1: NEUSPERA SNS SYSTEM MANUFACTURERS

Description	Manufacturer
Wireless Transmitter	Neuspera
Implantable SNS Kit (implanted stimulator & implant tools)	Oscor, Inc. 3816 DeSoto Blvd Palm Harbor, FL 34683 (USA)
Neuspera App for the Clinician Programmer	Velentium 22322 Grand Corner Drive, Suite 140 Katy, TX 77494 (USA)
Neuspera App for the Patient Controller	
Intraoperative Test Kit	Pro-Tech 14561 Marquardt Ave Santa Fe Springs, CA 90670 (USA)
Undergarment	Clothier Design Source 2408 W Territorial Rd St Paul, MN 55114 (USA) Jennifer Loel Designs 460 Aaron St, Suite B Cotati, CA 94931 (USA)
Wearable	TPI Custom Solutions 13828 Lincoln Street NE Ham Lake, MN 55304
Intraoperative (External) Stimulator	Biomedical Life Sciences 1954 Kellogg Avenue Carlsbad, CA 92008-6581
Charging Pad, Black	Samsung
Charging Pad, White	Samsung
Charging Pad, White	Belkin
Magnet	Neuspera

During Phase I of the trial, all undergarments were manufactured by Jennifer Loel Designs. This manufacturer is no longer providing undergarments for the clinical trial. A new manufacturer, Clothier Design Source, has developed a new women's undergarment design. Male subjects in the trial will be provided undergarments previously purchased and designed by Jennifer Loel Designs. Female subjects enrolled in Phase I of the trial received undergarments designed by Jennifer Loel Designs and could receive replacement undergarments manufactured by Jennifer Loel Designs or Clothier Design Source.

Female subjects in Phase II may receive undergarments from either Jennifer Loel Design or Clothier Design Source. All subjects may receive the Wearable as well as the undergarment.

2.5 Required Training and Experience

Clinicians who are trained by education in urology or urogynecology, have experience in treatment in OAB, urinary surgery, clinical studies, and Good Clinical Practice for Medical Devices (ISO 14155), ICH-GCP, applicable FDA Code of Federal Regulations (CFR), and are able to read and understand English qualify for the investigation. Sites will be selected based on completing a site qualification visit. Prior to the beginning of the clinical investigation, on-site initiation visits will be organized, in which full training will be given to all appropriate staff members participating in the clinical investigation. This training will include at least the following: instructions on the functions and use of the investigational device, procedures outlined in the clinical investigation plan, main principles of ICH-GCP and ISO 14155, overview of all investigational device units (including storage requirements and accountability instructions), instructions on completion of the case report forms, content of the investigator site file, and management of adverse events and serious adverse events.

Subjects will be trained on the use of the Neuspera SNS system by the clinical study staff and will be provided with the Patient Manual on operating the system.

2.6 Medical/Surgical Procedures

The Neuspera SNS neurostimulator implant procedure will be performed in accordance with approved Neuspera Intraoperative Kit Instructions for Use and Neuspera Implantable Sacral Nerve Stimulator Kit Instructions for Use for Model SNS-35 or Model SNS-28. Selection of the model number will be made at the time of the implant.

The subject will be prepped and will undergo local anesthesia, intravenous conscious sedation, or general anesthesia. The S3 foramen will be located per Neuspera's Implantable Sacral Nerve Stimulator Kit Instructions for Use. Following appropriate identification of the sacral nerve location, the neurostimulator will be implanted and stimulation parameters will be confirmed by observing motor responses of anal bellows with or without twitching of the big toe or movement in other toes. If motor responses are not confirmed at S3, the S4 foramen may be located, and motor response confirmed at this location. After confirming the functionality of all electrodes and optimal stimulation parameters, the tethering suture will be clipped, and the incision closed in accordance with approved Neuspera's Implantable Sacral Nerve Stimulator Kit Instructions for Use. A bandage will be placed over the implant site.

If appropriate physiological response cannot be achieved during the implant procedure, the neurostimulator will be removed and the subject will be followed for 30 days post procedure and exited from the study.

In Phase I, subjects determined to be SNS responders after the trial period had lateral and anterior/posterior radiographic images taken to confirm position of the neurostimulator at the final trial visit (day 21, 35 or 49).

In Phase II, all subjects will have lateral and anterior/posterior radiographic images taken to confirm position of the neurostimulator at Day 28 clinic visit (if determined a responder) or Day 42 clinic visit (responder or non-responder) post-implant.

2.7 Device Traceability

The Neuspera SNS System components will be identified and labeled by lot and/or serial number and will be traced for the duration of the clinical study. Each subject will be provided a Wireless Transmitter, Wireless Transmitter Charging Pad, Magnet, Patient Controller, and custom undergarments or Wearable. Additional Wireless Transmitters will be provided during the study should the subject have 4 hours of daily stimulation. See Section 13 for shipping, labeling, storage, and product accountability.

3 JUSTIFICATION FOR CLINICAL INVESTIGATION DESIGN

3.1 Prior Clinical Investigations

3.1.1 Acute Clinical Investigation

A prospective, acute, single center clinical study was conducted in six (6) subjects at the Maastricht University Medical Center in the Netherlands. The study was designed to evaluate Neuspera's Implantable SNS System in an acute setting. The study was approved by Maastricht University Medical Center Regional Ethics Committee.

The first primary objective of the study was to verify that energy could be transmitted from an external unit to the Neuspera Implantable SNS System, through a wireless connection, resulting in stimulation of the S3 sacral nerve. The second primary objective was to confirm that Neuspera's Implantable SNS System could be correctly placed and inserted in close proximity of the sacral nerve, in the S3 foramina. The secondary objective was to characterize the explant of the device after the intraoperative stimulation procedure. The safety objective was to assess the safety of the device during implantation, stimulation and explantation.

A total of 6 subjects signed an informed consent and were enrolled in the trial. All subjects were indicated for the Medtronic InterStim® procedure to treat their overactive bladder and passed all screening criteria for participation in the trial. One subject withdrew consent prior to the procedure and all remaining 5 subjects underwent the study procedure.

The Neuspera Implantable SNS System could be correctly placed in all subjects and a fluoroscopy image of the optimal position was obtained.

An obvious motor response was seen in 4 of the 5 subjects treated. The subject not showing a motor response to the stimulation had a high minimal threshold (5V) during stimulation with a foramen needle, exceeding the 2.4V stimulation voltage in Neuspera's Acute Human Study Implantable SNS System. This individual ultimately also proved to be a non-responder to the InterStim® device.

All 5 explant procedures were characterized as being performed successfully. The elapsed time in minutes between the end of the stimulation protocol and the moment the device was explanted from the body was on average 0.2 minutes with a maximum explant duration of 1 minute.

No device related, or procedure related adverse events, nor any device deficiencies, occurred during the course of the study.

The results of the clinical investigation demonstrate the feasibility of stimulating the S3 sacral nerve with a 2-part system using an external powering unit placed above an ultra-miniature implantable stimulator. The implant and explant procedures were performed successfully, and the safety results did not show any device related adverse events.

3.1.2 Phase I Clinical Results

The Phase I Clinical interim trial safety and efficacy results are summarized below. The safety results are from the 2023 FDA annual report with a data snapshot on 23 August 2023. The efficacy results are from an interim report based on a data cutoff date of 21 June 2021.

Of the 89 consented subjects, 39 were enrolled, and 34 of these were successfully implanted; five enrolled subjects had unsuccessful implant attempts. All 34 subjects implanted with the System completed the Trial Period and moved on into the Post Trial Period.

3.1.2.1 Efficacy

The mean number of UUIs per day was 4.1 ± 2.0 at baseline and decreased to 0.8 ± 0.9 at the Final Trial Visit, a mean decrease of 3.3 ± 1.7 UUIs per day from baseline. Of all implanted subjects, 88.2% (30/34) were responders (≥ 50% reduction in UUIs from baseline) at Day 21. Four subjects were not trial responders at Day 21. Of these, three subjects continued the trial period through Day 35, and 100% (3/3) were responders at Day 35. At the Final Trial Visit (Day 21 for *n* = 31, Day 35 for *n* = 3), 97.1% (33/34) of subjects were responders. One subject, initially thought to be a responder at Day 21, continued into the follow-up period at two hours per day of stimulation. The subject was later determined to be a non-responder at Day 21 and continued in the trial through 6-months of follow-up and was subsequently explanted as the subject was not satisfied with the therapy outcome.

The proportion of responders has continued to be statistically significantly greater than 50% during the follow-up period. The responder rates were 85.3% (*P*<0.0001) at Month 1, 90.0% (*P*<0.0001) at Month 2, 96.9% (*P*< 0.0001) at Month 3, 97% (*P*<0.0001) at Month 4, 78.6% (*P*= 0.0037) at Month 5, 88.5% (*P*<0.0001) at Month 6 and 100% (P=0.0002) at Month 9.

3.1.2.2 Safety

The safety results are from the 2023 FDA annual report with a data snapshot on 23 August 2023. Safety information is reported separately for Phase I and Phase II cohorts.

3.1.2.2.1 Phase I

There has been a total of 214 adverse events in 92.3% (36/39) of enrolled subjects; of these, there have been eight serious adverse events; all eight events were not related to the study device or study procedure. The majority of adverse events were mild or moderate in severity and were unrelated to the implant procedure or study device. A total of 32 adverse events reported in 15 subjects were related to the device and/or procedure. There were seven successful surgical revisions related to three device dislodgements and four device fractures. All subjects with device dislodgment and fractures remain in the study and are responding to the therapy post revisions. There have been twelve device explants. Three explants occurred after the database snapshot on 23 August 2023. Eleven subjects requested explant due to therapy not producing desired effect or unsatisfied with therapy or device performance, and one subject was explanted due to non-compliance.

To date, no serious adverse device effects (SADEs), unanticipated adverse device effects (UADEs), or deaths have been reported.

3.1.2.2.2 Phase II

There has been a total of 57 adverse events in 47.1% (33/70) of Implant Attempted subjects; of these, there was one serious adverse event (SAE), classified as respiratory failure, which was adjudicated as possibly related to the implant procedure and not related to the study device. The majority of adverse events were mild or moderate in severity (Clavien Dindo Classification I or II) and were unrelated to the implant procedure or study device. A total of 13 adverse events reported in 15.7% (11/70) Implant Attempted subjects were related to the device and/or procedure. Since the 23 August 2023 data snapshot, there have been 130 implant attempted subjects. In this group, there have been two device fractures in two subjects (1.5%), five clinically significant dislodgments in four subjects (3.9%), one dislodgement that was not clinically significant (0.77%), and four surgical revisions in four subjects (3.1%). There have been twelve (12) device explants. Overall, the number of fractures, migrations, and revisions observed are similar or below the rates seen for commercially available devices.

To date, no serious adverse device effects (SADEs), unanticipated adverse device effects (UADEs), or deaths have been reported.

3.1.2.2.3 Conclusion

Phase I of the study has demonstrated the preliminary effectiveness of 2 hours of daily stimulation duration with the Neuspera Implantable Sacral Nerve Stimulation System for the treatment of subjects with UUI who have failed or could not tolerate more conservative treatments. The type and rate of occurrence of adverse events are within the rates reported within the protocol and informed consents. The DSMB has reviewed all safety data included in the interim Phase I report, has provided recommendations on the daily stimulation duration that are consistent with the Phase II trial design, and supports the trial expansion to the pivotal Phase II.

Additionally, learning from Phase I of the trial has resulted in improvements of design and instructions for use that further mitigate risks of unsuccessful implants, implant movement and implant fracture. The undergarments for use in the trial have been redesigned, and programming parameters are well understood and standardized for use. The protocol has been modified to incorporate the intent-to-treat analysis for the primary efficacy endpoint, and processes are in place to maximize patient safety. Collectively all trial results and process improvements support expansion of the study to initiate the pivotal Phase II at 2 hours of daily stimulation with the option to increase to 4 hours of daily stimulation as needed.

3.2 Justification

The acute clinical investigation demonstrated the feasibility of implantation and stimulation of the S3 sacral nerve with a 2-part system using a wireless transmitting unit. Phase I of the clinical trial demonstrated the initial feasibility of the system in chronic use.

Phase I of the study characterized the human interaction with the wearable external Wireless Transmitter and associated system accessories. Phase I also demonstrated that short daily stimulation (2 hours per day) delivers appropriate urinary urgency incontinence symptom relief.

The purpose of Phase II, pivotal phase of this chronic study in human beings, is to evaluate the safety and efficacy of Neuspera's Implantable SNS System in the treatment of overactive bladder symptoms, specifically urinary urgency incontinence in patients who have failed or could not tolerate more conservative treatment. Based on the learning from Phase I of the trial, Phase II will be designed so that all subjects are trialed with 2-hours daily stimulation for 28 days, those subjects who are treatment responders (≥50% reduction in symptoms) will continue in the follow-up phase of the trial. As one subject in Phase I required 4-hours of daily stimulation to achieve response, Phase II of the trial will allow subjects with <50% reduction of symptoms to have the stimulation duration increased to 4-hours per day for an additional 14 days. This increase in duration of stimulation for subjects with less than 50% improvement in symptoms was also supported by the DSMB. All subjects regardless of response following 4-hours of stimulation duration will continue in the follow-up phase of the trial. Data from the Axonics ARTISAN-SNM trial as reported by McCrery,[6] indicates that some subjects who are non-responders at 1-month have demonstrated response at 6-months. Continuation of subjects who are non-responders after 4-hours of stimulation is based on subject informed consent. Non-responders, and any subject regardless of response, may withdraw consent to continue to participate in the study at any time.

The primary endpoint, defined as the percentage of all implanted subjects who experience an improvement in UUI symptoms of 50% or more (therapy responders) compared with baseline, will be assessed at 6-months of follow-up. The primary safety endpoint is defined as the incidence of device-related SAEs through the 6-month post-implant follow-up visit. Secondary endpoints will be assessed at both 6 and 12 months of follow-up. The sponsor intends to file a PMA submission at the end of the six-months of follow-up if the null hypothesis associated with the primary efficacy endpoint is rejected.

4 RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

The study protocol has been designed to provide the greatest benefits while assuring the safety of the participating subjects by mitigating the occurrence, limiting the severity and ameliorating the effects of any possible adverse events. The following describes the benefits subjects may receive as well as possible adverse events which have been identified as risks and for which subjects will be carefully monitored.

4.1 Anticipated Clinical Benefits

4.1.1 Direct Benefit

Subjects may potentially benefit from this study if they show improvement in overall medical condition, such as improvements in overactive bladder symptoms, and associated improvements in quality of life.

Potential benefits that may be associated with the investigational device that differ from current commercial products include:

A smaller implantable device with no pocket formation, no tunneling of the lead, or blunt dissection required, which may avoid complications associated with the other treatment options such as infection and pain. These complications are typically associated with creation of a pocket and battery presence and positioning for an implantable neurostimulator can and lead technology.
No implanted battery needing replacement which may result in fewer surgeries and complications associated with surgery.

4.1.2 Indirect Benefit

Subjects may indirectly benefit as a result of their participation in this study by helping researchers improve their understanding of the Neuspera Implantable SNS System. This research study allows the Sponsor and the Investigators to eventually help other subjects indicated for the same procedure.

4.2 Anticipated Adverse Device Effects

An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. Anticipated risks that may be associated with Neuspera's Implantable SNS System are noted in Section 4.4.

4.3 Residual Risks

In conducting the risk analysis, the concepts of risk estimation, risk acceptability, risk control and overall risk evaluation were applied in accordance with ISO 14971:2007. Based on an evaluation of residual risk acceptability, it was concluded that the overall residual risk did not exceed the criteria for acceptable risk.

4.4 Potential Risks that may be Associated with Neuspera's Implantable SNS System

Potential risks associated with the Neuspera Implantable SNS System based on a review of the literature and manuals for similar systems, the Neuspera Acute Human Study adverse events, and interim results from the SANS-UUI trial are listed in Table 2 below. Risks associated specifically identified in the Phase I Trial are noted in Table 3 and for Phase II in Table 4.

TABLE 2: POTENTIAL RISKS BASED ON LITERATURE REVIEW AND NEUSPERA CLINICAL DATA

Reported Adverse Events	Estimated Percent of Patients Reporting Event
Gastro-Intestinal Symptoms (abdominal pain, diarrhea, constipation, nausea, vomiting)	≥10%
Implant site infection	≥10%
Implant site pain	≥10%
Lead fibrosis	≥10%
Neurostimulator malfunction	≥10%
Neurostimulator migration	≥10%
Paresthesia	≥10%
Therapeutic product ineffective	≥10%
Undesirable change in stimulation	≥10%
Undesirable stimulation or sensations, including jolting or shock sensations	≥10%
Urinary tract infection	≥10%
Adverse change in bowel or voiding function	3% to <10%
Musculoskeletal discomforts including Muscle Tightness, Muscle Twitching, Muscle Contracture, Muscle Spasms, Musculoskeletal Pain, and Arthralgia	3% to <10%
Back pain	3% to <10%
Leg pain	3% to <10%
Falls	3% to <10%
Neurostimulator breakage or fracture	3% to <10%
Retained lead fragments	3% to <10%
Pain	3% to <10%
Pain in extremity	3% to <10%
Pollakiuria	3% to <10%
Seroma	3% to <10%
Dysuria, Urinary complications	1% to <3%
Genitourinary symptoms	1% to <3%
Granuloma	1% to <3%
Implant site hematoma, medical device site bruise	1% to <3%
Incision site complication	1% to <3%
Numbness	1% to <3%
Pelvic pain, Abdominal Pain	1% to <3%

Reported Adverse Events	Estimated Percent of Patients Reporting Event
Skin discomfort, irritation, redness, or a burn associated with use of an external charging/powering system	1% to <3%
Stroke	1% to <3%
Sciatica	1% to <3%
Urinary incontinence	1% to <3%
Accidental puncture	<1%
Allergic reaction to system components	<1%
Anal discomfort	<1%
Asthenia	<1%
Cellulitis	<1%
Change in sensation of Stimulation	<1%
Dermatitis contact, Skin Reaction	<1%
Discomfort	<1%
Dyskinesia	<1%
Fecal incontinence	<1%
Flank pain	<1%
Hypersensitivity	<1%
Implant site discharge	<1%
Implant site effusion	<1%
Implant site erosion	<1%
Implant site erythema	<1%
Implant site hematoma	<1%
Implant site irritation	<1%
Implant site pruritus	<1%
Implant site rash	<1%
Implant site reaction	<1%
Implant site scar	<1%
Implant site warmth	<1%
Incision site hemorrhage	<1%
Incisional hernia	<1%
Kidney Infection	<1%
Medical device complication	<1%
Micturition urgency	<1%
Nerve damage	<1%
Nocturia	<1%
Perineal pain	<1%
Post procedural complication	<1%

Reported Adverse Events	Estimated Percent of Patients Reporting Event
Post procedural pain	<1%
Pyrexia (fever)	<1%
Radiculopathy	<1%
Sacral pain	<1%
Sensory disturbance	<1%
Skin discoloration	<1%
Skin reaction	<1%
Therapeutic response decreased	<1%
Urinary incontinence	<1%
Vaginal pain	<1%
Wound dehiscence	<1%

The safety results are from the 2023 FDA annual report with a data snapshot on 23 August 2023. Safety information is reported separately for Phase I and Phase II cohorts.

Phase I enrolled subjects:

There has been a total of 214 adverse events in 92.3% (36/39) of enrolled subjects; of these, there have been eight serious adverse events; all eight events were not related to the study device or study procedure. The majority of adverse events were mild or moderate in severity and were unrelated to the implant procedure or study device. A total of 32 adverse events reported in 15 subjects were related to the device and/or procedure (see Table 3). There were seven successful surgical revisions related to three device dislodgements and four device fractures. All subjects with device dislodgment and fractures remain in the study and are responding to the therapy post revisions. There have been twelve device explants. Three explants occurred after the database snapshot on 23 August 2023. Eleven subjects requested explant due to therapy not producing desired effect or unsatisfied with therapy or device performance, and one subject was explanted due to non-compliance.

To date, no serious adverse device effects (SADEs), unanticipated adverse device effects (UADEs), or deaths have been reported.

TABLE 3. DEVICE AND/OR PROCEDURE RELATED ADVERSE EVENTS - ENROLLED SUBJECTS - PHASE I

Body System / Preferred Term[1]	Events n	Subjects n/N (%)
Total Device- or Procedure-Related Adverse Events	32	15/39 (38.5%)
Gastrointestinal disorders	2	2/39 (5.1%)
Abdominal pain	1	1/39 (2.6%)
Anal incontinence	1	1/39 (2.6%)

Body System / Preferred Term[1]	Events n	Subjects n/N (%)
General disorders and administration site conditions	10	7/39 (17.9%)
Implant site nodule	1	1/39 (2.6%)
Implant site pain	7	5/39 (12.8%)
Medical device site bruise	1	1/39 (2.6%)
Pain	1	1/39 (2.6%)
Musculoskeletal and connective tissue disorders	9	5/39 (12.8%)
Back pain	2	2/39 (5.1%)
Bursitis	1	1/39 (2.6%)
Muscle tightness	2	2/39 (5.1%)
Muscle twitching	1	1/39 (2.6%)
Musculoskeletal pain	1	1/39 (2.6%)
Pain in extremity	2	2/39 (5.1%)
Nervous system disorders	4	2/39 (5.1%)
Paraesthesia	1	1/39 (2.6%)
Sensory disturbance	3	1/39 (2.6%)
Product issues	3	3/39 (7.7%)
Device dislocation	2	2/39 (5.1%)
Device stimulation issue	1	1/39 (2.6%)
Renal and urinary disorders	1	1/39 (2.6%)
Urinary incontinence	1	1/39 (2.6%)
Skin and subcutaneous tissue disorders	1	1/39 (2.6%)
Erythema	1	1/39 (2.6%)
Surgical and medical procedures	1	1/39 (2.6%)
Therapy cessation	1	1/39 (2.6%)
Vascular disorders	1	1/39 (2.6%)
Hypotension	1	1/39 (2.6%)

[1]*As coded by the CEC chairperson.*

Phase II Implant Attempted subjects:

There has been a total of 57 adverse events in 47.1% (33/70) of Implant Attempted subjects; of these, there was one serious adverse event (SAE), classified as respiratory failure, which was adjudicated as possibly related to the implant procedure and not related to the study device. The majority of adverse events were mild or moderate in severity (Clavien Dindo Classification I or II) and were unrelated to the implant procedure or study device (see Table 4). A total of 13 adverse events reported in 15.7% (11/70)

Implant Attempted subjects were related to the device and/or procedure. Since the 23 August 2023 data cut-off, there have been 130 implant attempted subjects. In this group, there have been two device fractures in two subjects (1.5%), five clinically significant dislodgments in four subjects (3.9%), one dislodgement that was not clinically significant (0.77%), and four surgical revisions in four subjects (3.1%) There have been twelve (12) device explants. Overall, the number of fractures, migrations, and revisions observed are similar or below the rates seen for commercially available devices.

To date, no serious adverse device effects (SADEs), unanticipated adverse device effects (UADEs), or deaths have been reported.

TABLE 4. DEVICE AND/OR PROCEDURE RELATED ADVERSE EVENTS – IMPLANT ATTEMPTED SUBJECTS - PHASE II

Body System / Preferred Term[1]	**Events n**	**Subjects n/N (%)**
Total Device- or Procedure-Related Adverse Events	13	11/70 (15.7%)
Gastrointestinal disorders	4	3/70 (4.3%)
Dysphagia	1	1/70 (1.4%)
Frequent bowel movements	1	1/70 (1.4%)
Haematemesis	1	1/70 (1.4%)
Vomiting	1	1/70 (1.4%)
General disorders and administration site conditions	2	2/70 (2.9%)
Implant site pain	1	1/70 (1.4%)
Medical device pain	1	1/70 (1.4%)
Musculoskeletal and connective tissue disorders	2	2/70 (2.9%)
Back pain	1	1/70 (1.4%)
Pain in extremity	1	1/70 (1.4%)
Nervous system disorders	1	1/70 (1.4%)
Radicular pain	1	1/70 (1.4%)
Product issues	2	2/70 (2.9%)
Device stimulation issue	2	2/70 (2.9%)
Renal and urinary disorders	1	1/70 (1.4%)
Micturition urgency	1	1/70 (1.4%)
Respiratory, thoracic and mediastinal disorders	1	1/70 (1.4%)
Respiratory failure	1	1/70 (1.4%)

[1]*As coded by the CEC chairperson.*

Wireless Transmitter - Surface Skin Heating

The Wireless Transmitter must be worn in the pocket of the Neuspera undergarment or Wearable. This is to protect the subject from the heat of the Wireless Transmitter and to position it correctly to power the neurostimulator. Wearing the Wireless Transmitter directly against skin may result in discomfort, irritation, or a burn. Instruct the subject to not lie on the Wireless Transmitter or wear it while sleeping.

It is normal for the Wireless Transmitter to become warm during use as it is delivering power to the neurostimulator. If it becomes uncomfortably hot, the subject will be instructed to turn it off. If it is too hot to keep wearing the device, the subject will be instructed to take off the undergarment or Wearable and contact the investigator/clinic.

Lack of Stimulation

The subject may be a non-responder to SNS therapy, or the study device may fail to adequately induce therapeutic response.

Procedural Risks

Standard risks associated with minor surgery, including side effects from anesthesia, post-procedural pain or discomfort, and complications at the incision/injection site such as infection, bleeding, bruising, or swelling, may occur due to the neurostimulator implantation procedure.

Unknown Risks

There may also be risks that are unanticipated at this time.

Concomitant Medication

There are no identified risks associated with concomitant medication and the Neuspera SNS System.

4.5 Contraindications

Electrical treatments where the conducted current is induced into the body from an external source into the area of the implant (this may permanently damage the implant).

Medical treatments or procedures utilizing effects caused by electric fields (such as diathermy) unless the treatment or procedure is identified as acceptable.

4.6 Risk Control/Mitigation

Risk management methods will be followed for the study. The manners in which risks will be minimized include the following:

- In response to the device dislodgements and fractures noted in Section 4.4, Neuspera implemented three mitigations. These improvements are expected to reduce the risks of device dislodgement and fracture in Phase II of the clinical trial.
  - A shorter version of the implantable device was created for subjects with thinner sacra.
  - The implant instructions for use were revised to instruct implanters to place the devices deeper within sacral foramen to ensure that the proximal tines of the device are

implanted in more anchorable tissue. The shorter device and deeper placement of implants are primary mitigators to prevent device movement and to keep the neurostimulator within the sacral foramen along the sacral nerve. The epoxy strain relief joint, which was subject to fracture, will then remain within the protection of the foramen.

- As a secondary mitigation, the length of overlap of epoxy in the strain relief joint was increased to improve the mechanical integrity of the epoxy / array interface. The increase in overlap improves the resistance to shear and bending loads if the implant moves outwards and exposes the epoxy strain relief joint.

- The Investigator and clinical site staff were chosen because of their expertise in the management of OAB and use of sacral nerve stimulation for the treatment of OAB.
- The physicians performing device-related procedures have received the appropriate training in the use of the device.
- Subjects are being monitored/observed throughout the study by multiple-disciplinary site staff, trained in the management of subjects with OAB.
- Investigators will discuss the signs and symptoms that each subject should be made aware of with respect to a potential adverse event. Additionally, each subject will be sent home with a copy of the informed consent which provides details regarding the signs and symptoms to be aware of with respect to a potential adverse event. These signs and symptoms will be reviewed with the subject at the time the informed consent is signed. Subjects will be encouraged to notify the site if they have concerns about signs and symptoms they are experiencing. They may be instructed to come to the clinic/hospital for further evaluation and/or treatment if further assessment is needed.
- Pre-clinical testing has been performed in order to optimize the device safety and function.
- Field Clinical Engineers may be present during implants in order to provide training and support.
- Experienced Clinical Monitors will perform on-site and remote monitoring throughout the study to ensure protocol compliance and compliance with GCP, ISO 14155, FDA regulations, IRB/EC requirements and other regional regulations.
- Ongoing monitoring of study data and results, including the use of an independent Clinical Events Committee, comprised of physicians knowledgeable in the procedure and treatment of subjects with OAB.
- An independent Data Safety Monitoring Board (DSMB) will serve as an advisory group to the Sponsor/CRO and will review aggregate Phase I and Phase II data. The DSMB will assure the safety and welfare of the study subjects and ongoing validity and scientific merit of the study.
- Study stopping rules have been put in place to be followed by the DSMB. These stopping rules have been added to Section 6.4 of the protocol.
- All subjects will be provided with an identification card (ID) indicating they have an investigational device implant and phone number to call in case of emergency. Figure 14 presents a sample ID card.

FIGURE 14: SUBJECT IDENTIFICATION CARD

Furthermore, potential risks associated with participation in this investigation will be minimized and managed in accordance with applicable regulations, and requirements of the approving Institutional Review Board(s)/Ethics Committee(s).

4.7 Risk-to-Benefit Rationale

Any potential risk presented by this clinical investigation has been minimized and adequate testing, safeguards, and safety monitoring have been incorporated into the clinical investigation to further minimize and mitigate the risks. The benefits of Neuspera's Implantable SNS System outweigh the potential risks posed to participating subjects.

5 OVERALL STUDY DESIGN

5.1 Study Purpose

The purpose of this seamless phased study is to test the overall safety and efficacy of the Neuspera Implantable SNS System in the treatment of overactive bladder symptoms, specifically UUI in subjects who have failed or could not tolerate more conservative treatment.

5.2 Study Overview

This is a prospective, multi-center, single-arm, seamless phased pivotal clinical study using the Neuspera Implantable SNS System for treatment of UUI in subjects who have failed or could not tolerate more conservative treatment.

The study will be conducted in two phases. Phase I has been used to understand the initial usability of the system and to determine the daily stimulation parameters for Phase II. Enrollment in Phase I has been completed and all implanted subjects are in the follow-up phase. All enrolled subjects did undergo a SNS trial period to test their clinical response to sacral nerve stimulation. Stimulation started with 2 hours of stimulation per day, and in 1/34 enrolled subjects, stimulation was extended to 4 hours per day. The trial was designed to allow up to 8 hours of stimulation if 4 hours was not successful, but no subject required 8 hours of stimulation to achieve a therapeutic response (≥50% reduction of symptoms when compared to baseline).

Phase I

All Phase I subjects will continue to be followed until regulatory approval, estimated to be up to 60 months post-trial period. Figure 15 below details subject flow for Phase I of the study based on the initial trial design. As noted, no subjects received 8-hours of stimulation in Phase I of the trial.

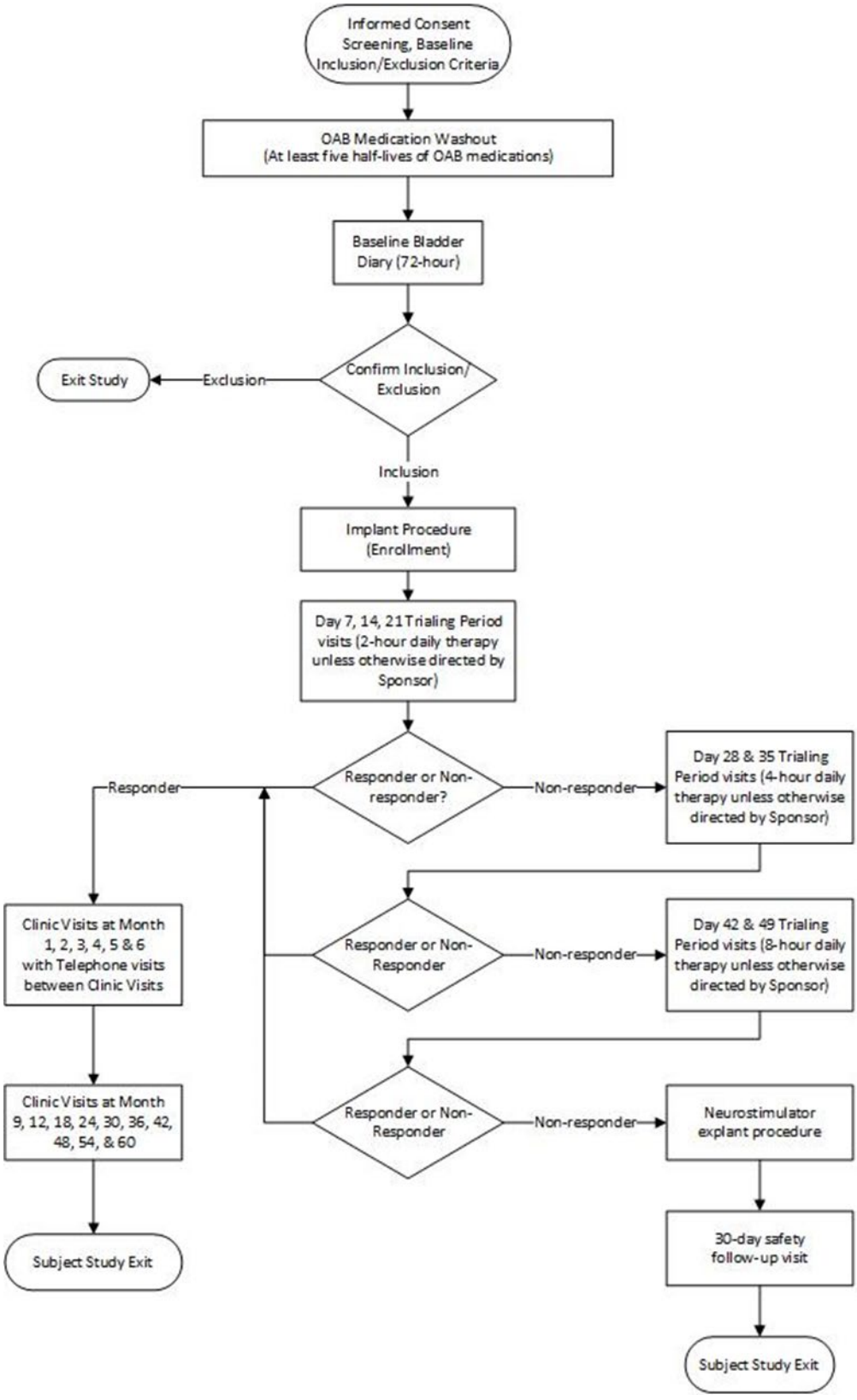


FIGURE 15: PHASE I SUBJECT FLOWCHART

Phase I Sub-Study: There is a sub-study to investigate the effectiveness and subject acceptance of half-hour daily stimulation to treat UUI. The details are provided in Appendix A: Phase I Sub-Study.

Phase II

Figure 16 below details subject flow for Phase II of the study. Results of Phase I were used to determine the number of hours of daily stimulation per day in Phase II. In Phase II, during the first 28 days, subjects will receive 2 hours of continuous daily stimulation using the external Wireless Transmitter. At the end of 28 days treatment efficacy will be assessed. Subjects with acceptable efficacy (≥50% reduction in number of UUI episodes) will be considered a responder and will continue in the post-implant follow-up with 2 hours of daily stimulation using the Wireless Transmitter. Those with less than acceptable efficacy (<50% reduction in number of UUI episodes) will continue for an additional 14-day period with 4 hours of daily stimulation with the Wireless Transmitter. After 14 days of 4 hours of daily stimulation those subjects with ≥50% reduction in number of UUI episodes will be considered a responder. As the primary efficacy endpoint is based on intent-to-treat analysis, all implanted subjects, regardless of responder or non-responder status at the end of the 42-day period will continue in the post-implant follow-up with 4 hours of daily stimulation. A decision to continue a subject with less than a 50% improvement at the end of the 42-day period will be made by the investigator based on what they determine is in the best interest of the subject. All implanted subjects will be followed until regulatory approval is achieved, estimated to be up to 36 months. When stimulation is not sufficient, subjects may leave the trial at any time. At such time, device explant procedures will be followed (Section 7.5.8.10).

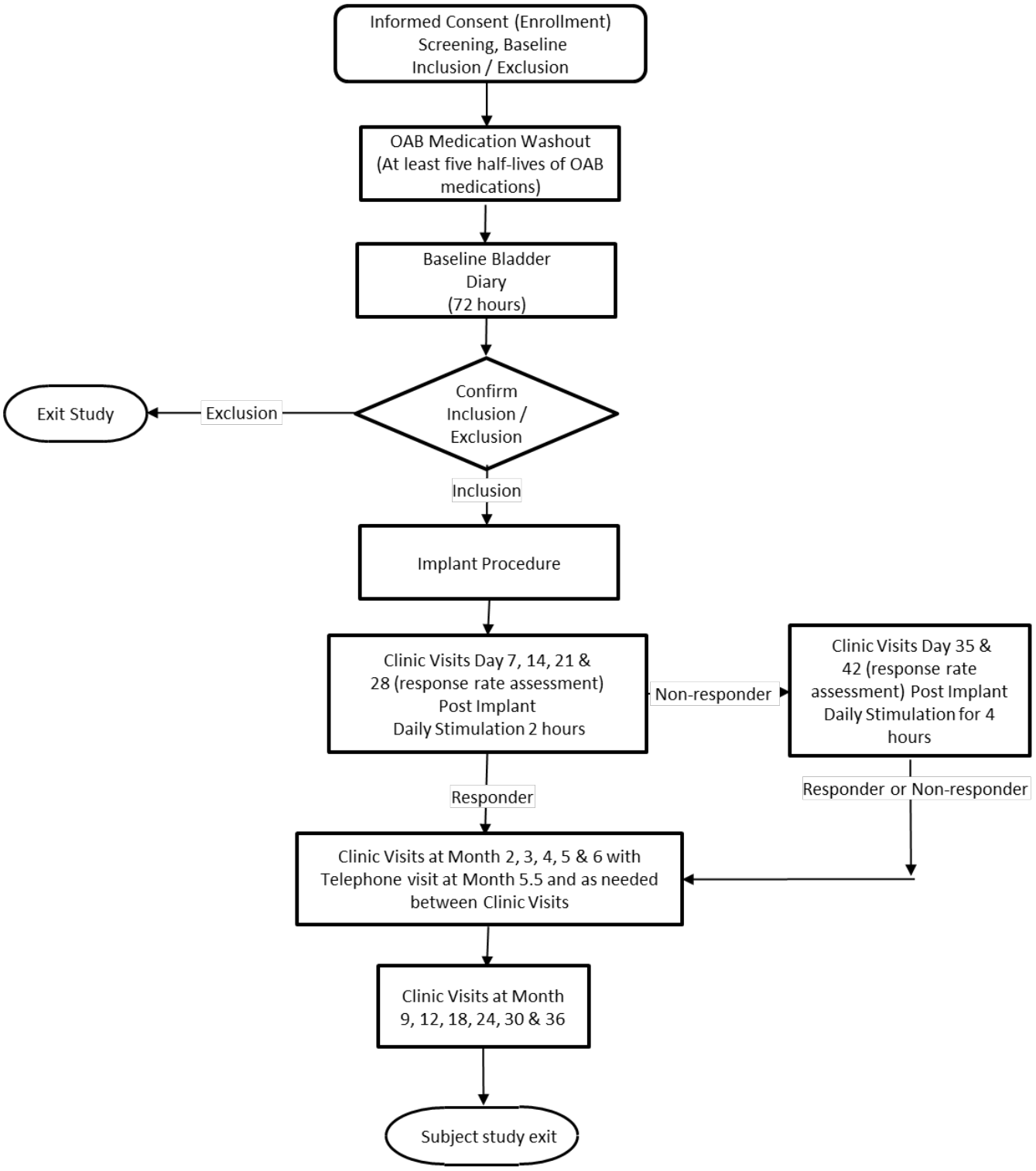


FIGURE 16:PHASE II SUBJECT FLOWCHART

5.3 Study Duration

The enrollment period is expected to take approximately 12 months for Phase II. The total expected duration of the clinical trial is dependent on the length of time to regulatory approval. Implanted subjects from Phase I and Phase II will continue to be followed until US PMA approval. Health Canada approval, European approval, CE Mark, may be achieved earlier or later than PMA approval. If achieved earlier, all Canadian and EU subjects will continue to be followed in the trial until US PMA approval is achieved which is estimated to be up to 36 months or longer for some subjects. Subjects enrolled earlier will have a longer follow-up than subjects enrolled later. In Phase II, subjects enrolled later may be followed for less than 36 months but at least until the 12-month follow-up visit is completed. It is estimated that the first subjects enrolled in Phase II will be in the study approximately 3 years. If Neuspera determines regulatory approval will not be achieved, the study will be closed.

5.4 Minimization of Bias

The potential for bias during this study has been minimized by the clinical study design that is expected to be conducted under the terms of the approved study protocol. The following methods have been incorporated into the study protocol to minimize potential bias:

- Subjects will be screened to confirm eligibility for implant with defined inclusion/exclusion criteria prior to procedure.
- All sites will use the same version of the protocol and data collection materials.
- The study contains pre-defined endpoints, analyses, and success criteria.
- All study and Sponsor personnel will be trained on their respective responsibilities for the study using standardized training materials.
- All study personnel will be trained on and are required to follow the protocol.
- All study investigators will be required to comply with 21 CFR Part 54 and Financial Disclosure by Clinical Investigators.
- Experienced Clinical Monitors will perform on-site and remote monitoring throughout the study to ensure protocol compliance and compliance with GCP, ISO 14155, FDA and IRB/REC regulations.
- Ongoing monitoring of adverse events, including the use of an independent Clinical Events Committee, comprised of physicians knowledgeable in the procedure and treatment of subjects with OAB.
- A Data Safety Monitoring Board will serve as an independent advisory group to the Sponsor/CRO managing Neuspera's Implantable Sacral Nerve Stimulation System clinical study to assure the safety and welfare of the study subjects and ongoing validity and scientific merit of this study.
- Study stopping rules have been put in place to be followed by the DSMB. These stopping rules have been added to Section 6.4 of the protocol.

6 STATISTICAL CONSIDERATIONS

6.1 Objectives, Endpoints and Analysis

The overall objective of the study is to assess the safety and efficacy of the Neuspera Implantable SNS System based on Phase II results, following the determination of daily stimulation settings as informed by Phase I. Accordingly, hypotheses and formal endpoints are primarily based on results of Phase II. Unless otherwise specified, all analyses described in this section refer to the analysis of data gathered only under Phase II. Analyses for Phase I will consist of descriptive statistics since stand-alone definitive conclusions regarding safety or efficacy from this phase are not desired, and the purpose of Phase I is simply to inform stimulation settings for Phase II. The Statistical Analysis Plan (SAP) for this study provides additional details.

6.1.1 Analysis Populations

Intent-to-Treat (ITT) Analysis Set: The ITT analysis set is defined as all Phase II subjects who have signed informed consent. Demographic information and study exit details will be reported separately for those subjects included in the ITT population where no initial implant was attempted.
Modified Intent-to-Treat (mITT) Analysis Set: The mITT analysis set is defined as all Phase II subjects for whom an initial implant is attempted. The mITT analysis set is the primary analysis set for assessment of primary endpoints.
Implanted Analysis Set: The Implanted analysis set is defined as all Phase II subjects who are implanted with the Neuspera SNS system.
Responder Analysis Set: The Responder analysis set is defined as subjects who are implanted with the system and are defined as responders at Day 28 or Day 42 clinic visit post-implant.
Per Protocol (PP) Analysis Set: The Per Protocol analysis set is defined as implanted subjects who have no protocol deviations that may significantly affect the primary endpoints. The determination of subjects excluded from Per Protocol analysis set will be made prior to analysis.

6.1.2 Primary Efficacy Objective, Endpoints, and Analysis

6.1.2.1 Primary Efficacy Objective

To test the efficacy of the Neuspera Implantable SNS System for treatment of UUI.

6.1.2.2 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the percentage of subjects who experience an improvement in UUI symptoms of 50% or more (therapy responders). A therapy responder is defined as experiencing ≥50% reduction in the number of UUI episodes at 6-months post-implant, relative to the number of UUI episodes at baseline.

Calculation of the primary efficacy endpoint will be based on the mITT analysis set.

6.1.2.3 Primary Efficacy Analysis

The statistical hypothesis test for the primary efficacy endpoint will be based on comparing the percentage of subjects with at least 50% improvement in UUI symptoms (therapy responders) to a null

value of 50%, the same performance goal as in the study by McCrery et. al.[6] Mathematically, the null and alternative hypothesis are stated as:

Ho: $p \leq 0.50$

Ha: $p > 0.50$

The null hypothesis will be rejected at the 0.025 alpha level based on a one-sided, one sample exact tests of binomial proportions for responders. The proportion of 0.50 for responders corresponds to a value of 50%. Study success is defined as successful rejection of the null hypothesis.

The 50% reduction in UUI symptoms treats subjects as their own control and is based on a clinically meaningful improvement at the subject level in the primary efficacy endpoint.[4-6] Successful rejection of the null hypotheses will indicate a clinically meaningful result in the majority of subjects by a statistically significant amount. Success for the statistical test will require that the lower confidence bound for the percentage of subjects with at least 50% improvement in UUI symptoms (therapy responders) will exceed 50%. This means practically, that the percentage of subjects with at least a 50% improvement must be substantially greater than 50% in order for the lower confidence bound to exceed 50%. For example, with an evaluable sample size of implanted subjects, the "worst case" results that would still meet the statistical threshold for this performance goal would be 72 out of 120 (60%). Additionally, the study is powered around an assumed population responder rate of 63.5% or higher.

The primary analysis population for the primary efficacy endpoint is the mITT Analysis Set. The primary efficacy endpoint will also be evaluated in the Implanted analysis set, the Responder analysis set, and the Per Protocol analysis set (without imputation for missing data) to assess the robustness of results. If there are no differences between analyses sets (e.g., Implanted and Responder analysis sets include all the same subjects), separate analyses will not be presented. Analyses of the primary efficacy endpoint for all analysis populations will be conducted after 6-month post-implant follow-up is completed for all subjects.

For the primary efficacy endpoint, subjects withdrawing for reasons related to a lack of efficacy or due to an adverse event (including death) will be counted as failures. Also, those subjects who take OAB medications (after the first two weeks following implant) and prior to the six-month visit should be adjudicated as device failures. For subjects with missing primary efficacy endpoint results for other reasons (missing diary, subject loss-to-follow-up, etc.), multiple imputation will be used to impute the outcome and results from the imputed data sets combined appropriately to preserve valid inference. Details of the multiple imputation are provided in the Statistical Analysis Plan.

The primary efficacy endpoint will be presented by study visit with descriptive statistics and nominal 95% confidence intervals.

6.1.3 Primary Safety Objective, Endpoint and Analysis

6.1.3.1 Primary Safety Objective

The primary safety objective of the study is to assess the safety of the Neuspera Implantable SNS System for treatment of UUI.

6.1.3.2 Primary Safety Endpoint

The primary safety endpoint is defined as the incidence of device-related SAEs through the 6-month post-implant visit. The analysis of the endpoint is the proportion of subjects experiencing device-related SAEs through the 6-month post-implant visit.

6.1.3.3 Primary Safety Analysis

There is no planned statistical hypothesis test for the primary safety endpoint. The proportion of subjects experiencing an event, as well as the numerator and denominator, and the associated two-sided exact 95% binomial confidence interval will be provided. Values will be expressed as percentages.

The primary analysis population for the primary safety endpoint is the mITT analysis set as defined in Section 6.1.1. Subjects who exit the study prior to reaching the 6-month post-implant follow-up visit without experiencing a device-related SAE will be assumed free of such an event.

Any adverse events reported for enrolled subjects who are excluded from the mITT analysis set will be reported separately for the duration of the study.

6.1.4 Interim Analyses

The Sponsor will use Phase I, feasibility phase, of the trial to assess system performance, subject compliance, and determination of the daily stimulation duration for Phase II. Phase I data will also be examined as needed to determine if modifications need to be made to training of the centers on implant technique, subject instructions, duration of stimulation, etc. Formal statistical conclusion from Phase I will not be made so there are no type I error concerns.

For Phase II, there are no planned interim analyses for the purpose of adaptive study modifications or early stopping for success. An interim analysis will be performed when the 60th Phase II subject has completed the 3-month post implant visit. For this interim analysis, the primary and secondary safety and effectiveness endpoints will be assessed, but at the three-month timepoint. This interim analysis will be used for business purposes only, no modifications to the study will be made based on this analysis, and outcomes will not be published or shared with investigators, patients, or Neuspera employees with direct subject access. The study will be completed to the planned sample size of 120 attempted implants regardless of the outcome of the interim analysis. Operational bias will be minimized by having a third party, independent statistician separate from study operational personnel and study statistician, who will perform the interim analysis.

6.1.5 Secondary Endpoints

The secondary endpoints include the following, assessed at both 6- and 12-months post-implant visits unless specified otherwise:

- Change from baseline in quality of life as measured and assessed by the total ICIQ-OABqol score.
- Change from baseline in mean number of UUI episodes.
- The percentage of subjects who experience an improvement in UUI symptoms (therapy responders) of at least 50% or more at 12 months visit post implant.

- The percentage of subjects who experience an improvement in ICIQ-OABqol of at least 10 points.[8]
- Change in urgent voids per day calculated across all diary episodes with at least mild urgency.
- Change in average number of daily voids from baseline in subjects with at least 8 voids at baseline.
- Change in quality of life measured from baseline as measured and assessed by the ICIQ-OABqol subscale scores.
- Comprehensive summary of all adverse events (AEs) for the duration of study participation.
- Device parameters including but not limited to voltage, pulse width, frequency, and stimulating electrode.
- Physician and subject satisfaction as assessed with the User Experience Questionnaire at 6-month visit post implant.
- Change in Male/Female Lower Urinary Tract Symptoms questionnaire.
- The percentage of subjects with device-related serious adverse events reported through 12-month visit post-implant.
- Change in total urinary output as measured by 72-hour bladder diary.
- Change in fecal incontinence as measured by the Wexner Scale compared to baseline. Calculated in subjects with fecal incontinence.
- Patient Global Impression of Improvement (PGI-I) measured after implant during follow-up.

Secondary endpoints will be summarized across study visits. Type I error control for testing of secondary endpoints intended for labeling claims is described in section 6.1.6.2.

6.1.6 Phase II Analysis of Secondary Endpoints

6.1.6.1 Analysis of Secondary Efficacy Endpoints That May Be Used for Labeling Claims

The type I error for the primary efficacy endpoint and for a subset of secondary endpoints will be controlled via hierarchical testing. The following secondary endpoints will be included in a hierarchical analysis of study endpoints and may be intended for labeling claims (all at 6-month visit post-implant follow-up):

- Change from baseline in mean number of UUI episodes
- Change from baseline in ICIQ-OABqol score
- The percentage of subjects who experience an improvement in ICIQ-OABqol of at least 10 points
- Change in urgent episodes per day from baseline. Calculated across all diary episodes with at least mild urgency
- Change in average number of daily voids in subjects with at least 8 voids at baseline
- Change in fecal incontinence as measured by the Wexner Scale compared to baseline. Calculated in subjects with fecal incontinence.

The primary efficacy endpoint will be analyzed with a one-sided test at the α = 0.025 level. To maintain the overall type I error rate, testing of these secondary hypotheses will only proceed if the analysis for the primary efficacy endpoint is statistically significant (one-sided $p < 0.025$). If the primary efficacy analysis is not statistically significant (one-sided $p \geq 0.025$), these secondary endpoints will not be formally tested, and analysis of these endpoints will be considered exploratory.

Provided that the primary endpoint analysis is statistically significant, testing will proceed to the secondary endpoints included in the hierarchical analysis. Performance goals for each secondary endpoint that may be used for labeling claim are included in the statistical analysis plan (SAP). Testing will proceed in the order specified above with each endpoint tested sequentially. If the analysis of the secondary endpoint under consideration is statistically significant (one-sided $p < 0.025$), the result for that endpoint is declared statistically significant, and testing proceeds to the secondary endpoint next in the order. As soon as an analysis is not statistically significant (one-sided $p \geq 0.025$), that endpoint is declared statistically non-significant, further testing of these secondary endpoints is terminated, and no formal statistical conclusion is reached on the remaining endpoints, irrespective of their observed p-values.

The sponsor intends to file a PMA submission at the end of the six-months of follow-up if the null hypothesis associated with the primary efficacy endpoint is rejected. This will include analysis of the primary endpoint and the first secondary endpoint in the hierarchical sequence. If the analysis of the first secondary endpoint is statistically significant, the remaining secondary endpoints in the sequence will be analysed in order when the data are available.

6.1.6.2 Analysis of Secondary Efficacy Endpoints Not Intended for Labeling Claims

Analysis of secondary endpoints not intended for labeling claims, (i.e., those not included in the hierarchical testing) will be considered exploratory in nature. Each of these endpoints will be tested at the α = 0.05 level using a two-sided test with no adjustment for multiplicity. Any p-values from these analyses will not be reported in the labeling.

6.2 Sample Size Determination

Sample size for Phase II is based on power requirements for the primary efficacy endpoint. A total of 120 attempted implants will provide over 85% power for a one-sided 0.025 exact binomial test against the null hypothesis assuming that 1) the implant success rate is 95%, 2) subjects in whom an implant is attempted but is not successful are counted as failures, and 3) the overall responder rate, including failed implant attempts, is 63.5%. Calculations are based on a one-sample, one-sided exact test of binomial proportions with a normal approximation and were performed with PASS 2019. To account for potential attrition prior to implant of up to approximately 43% including screen failures, up to 255 subjects will be enrolled/consented in Phase II. Revisions will not count towards attempted implants.

Sample size at any one investigational site will be restricted to no more than 25 subjects implanted for Phase II. Consideration will be given to lifting the 25 subject implanted cap in Phase II if the investigator makes a request of the sponsor.

6.3 Analysis of Replacements, Explants

During the course of the study, it may be necessary for the investigational device to be replaced or permanently explanted from the subject. Revision rates in the literature range from 4% in the InSite study[4] to 33% in the Herbison[9] study. Depending on the timing of replacements, it may be necessary for the subject's response rate to be reassessed in the first 28 to 42-days post-implant.

During Phase I of the study, if a subject receives a neurostimulator replacement prior to Month 3 clinic visit, the subject will restart their follow-up schedule, and repeat the trialing period and any of the follow-up visits completed prior to replacement. If a subject receives a device replacement prior to the assessment of the primary efficacy endpoint in Phase II (Month 6 clinic visit), the subject will restart their entire follow-up schedule post-implant, including the responder rate assessments at Day 28 and Day 42, if not a responder at Day 28. The date of replacement will be considered the new Device Implant date for analysis and follow-up purposes. If a device replacement is required after the follow-up periods indicated above, subjects will continue on their original follow-up schedule and will not repeat any of the assessments or follow-up visits already completed.

If assessment of the response rate is repeated in the first 28 to 42-days post-implant, data collected after the most recent implant will be used in the analysis. Similarly, if the subject is required to repeat any portion of the post-implant follow-up visits after a replacement (replacement occurred before Month 6 clinic visit), the data from the replacement visit(s) will be used in analysis. The date of replacement will be considered the Device Implant date for analysis and follow-up purposes. A subject is only allowed to repeat any portion of the post-implant period once.

If the device is permanently explanted prior to the assessment of the primary efficacy endpoint for any reason, the subject will be considered a failure for the primary efficacy analysis.

6.4 Study Stopping Rules for Phase II

Phase II will use stopping rules designed to suspend enrollment and trigger a series of events if at any time there is sufficient statistical evidence to conclude that any of the Phase II probabilities of device fracture, device dislodgement/migration, or surgical revision exceed comparator probabilities from an approved device. The comparator probabilities are shown in Table 5.

TABLE 5: COMPARATOR EVENT PROBABILITIES GUIDING THE PHASE II STOPPING RULE. VALUES SHOWN ARE POINT ESTIMATES (UPPER LIMITS OF 95% CONFIDENCE INTERVALS).

Event Type	Proportion of Subjects with Event
Fractures	0.014 (0.022)[1]
Dislodgements/Migrations	0.026 (0.036)[2]

[1] Based on Medtronic's 2020 Product Performance Report showing 19 subjects experienced lead fractures out of 1,314 subjects followed (page 167).

[2] Based on Medtronic's 2020 Performance Report showing 34 subject experienced lead dislodgements/migrations out of 1,314 subjects followed (page 167).

Surgical Revisions	0.118 (0.239)[3]

Phase II will use the following stopping rule. At each occurrence of device fracture, dislodgement/migration, or surgical revision, form an exact one-sided binomial confidence interval for the event probability. Determine whether any of the following conditions is met:

- The lower limit of the interval for device fractures exceeds 0.014.
- The lower limit of the interval for device dislodgements/migrations exceeds 0.026.
- The lower limit of the interval for surgical revisions exceeds 0.118.

The numerator for each event is the number of subjects who have experienced the event up to that time. The denominator will be the number of subjects implanted up to that time. For device fractures and migrations/dislodgements, the confidence level of the interval will be 95%. For surgical revisions, the confidence level will be 80% if 50 or fewer subjects have been implanted; if more than 50 subjects have been implanted, the confidence level will be 95%. If any of the above conditions is met, the following actions will be taken:

- Both enrollment and implants will be suspended, and FDA will be notified within 7 days
- Neuspera will conduct a root cause analysis to determine the cause of the safety events that triggered the stopping rule
- Neuspera will prepare a safety report for submission to the DSMB
- The DSMB will convene, review the safety report and root cause analysis, and make a recommendation on study continuance (continue enrollment post FDA review and approval, continue enrollment suspension pending FDA decision and/or further investigation by the sponsor, etc.)
- Neuspera will submit to FDA the safety report, the root cause analysis, and the DSMB's recommendation
- FDA will make final determination on study continuance

The stopping rules will take effect only when more than 15 subjects have been implanted. After more than 15 subjects have been implanted, all events, including any events within the first 15 subjects will be counted in assessing the criteria for stopping. However, if there are 4 or more surgical revisions when 15 or fewer subjects have been implanted, the stopping rule is triggered once the 4th surgical revision occurs. Additional subjects will not be implanted in the scenario that the stopping rules will automatically be triggered at subject 16 (i.e., 4 surgical revisions occur in the first 15 subjects).

[3] Based on Medtronic Clinical Summary Report stating 6 out of 51 subjects had "surgical procedures to resolve adverse events or technical observations, or due to lack of efficacy from the time of test lead implant to 6-month follow-up after full system implant" (page 16).

The use of an 80% confidence level as compared to 95% early in the study for surgical revisions makes it more, not less, likely that enrollment would stop due to surgical revisions in the event that revision rates are unacceptably high.

6.5 Deviations to the Statistical Analysis Plan

If there are any deviations to the Statistical Analysis Plan, this will be noted in any interim and final reports for the trial.

7 DESIGN OF THE CLINICAL INVESTIGATION

7.1 General

The study is a prospective, multi-center, seamless, single-arm, pivotal clinical study assessing the safety and efficacy of Neuspera's Implantable SNS System in subjects with symptoms of UUI. The Neuspera Implantable Sacral Nerve Stimulation System Investigator's Brochure is available upon request from the Sponsor.

The seamless, single-arm study is designed in two phases: Phase I, feasibility phase and Phase II, pivotal phase. The feasibility phase was to assess the utilization and performance of the system during the SNS trial and follow-up periods and to help plan and inform the pivotal trial design, including the length of hours of daily stimulation to be used in Phase II of the trial. The Phase II, pivotal phase, is a confirmatory investigation to collect safety and efficacy data on the performance of the overall system.

As this is a clinical trial evaluating an investigational sacral nerve stimulation system, there are baseline screening criteria, sacral nerve stimulation trialing procedures, implant procedures and follow-up procedures that deviate from screening criteria and procedures for commercially available systems. Commercially available sacral nerve stimulation devices require subjects to have failed or be intolerable to more conservative treatments. Eligible subjects receive a peripheral nerve evaluation implant, typically 7 days, or a staged trial with a tined lead, typically 2-3 weeks, to evaluate the subject's response to sacral nerve modulation. Post implant follow-up consultation in the first year typically occurs at 1, 6 and 12 months.[11] In the clinical trial design, the inclusion and exclusion criteria requires some clinical testing or therapy restrictions that may not be required in general clinical practice. Likewise, the additional follow-up visits post implant are required by the study design and are outlined in the remainder of this section. The additional testing and follow-up visits deviate from general clinical practice SNS therapy due to the investigational nature of the system under study.

Enrollment in Phase I is closed. Should an enrolled subject require a replacement before the 3-month clinic visit, the subject will undergo a repeat SNS trial period testing their clinical response for approximately 21 days. During the first SNS trial period, subjects will have 2 hours of continuous stimulation with Neuspera's SNS System. Subjects who are responders (≥50% reduction in UUI episodes compared to baseline) will continue to the post-trial phase with 2 hours of daily therapy. Subjects who have <50% reduction in UUI episodes will continue in the trial period with 4 hours of continuous daily therapy for 14 days. Following the additional 14 days of trial, response rate will be determined. Subjects who have ≥50% reduction in UUI episodes compared to baseline will proceed to the post-trial period with 4 hours of continuous daily therapy. Subjects who have <50% reduction in UUI episode will continue in the trial period with 8 hours of continuous daily therapy for 14 days. Following the additional 14 days of trial, response rate will be determined. Subjects who have ≥50% reduction in UUI episodes will proceed to the post-trial period with 8 hours of continuous daily therapy. Subjects who have <50% reduction in UUI episodes are deemed non-responders. The subject may discuss alternative therapy options with the investigator to determine if the neurostimulator will be removed. Subjects may remain in the trial at 8 hours of continuous stimulation. If the subject and the investigator determine that it will be in the subject's best interest the neurostimulator may be removed. The Neuspera Wireless

Transmitter(s), Wireless Transmitter Charging Pad, Magnet and Patient Controller will be returned to the clinic. Subjects may dispose of used custom undergarments or Wearable at their discretion. These subjects will return to the clinic approximately 30 days for a safety evaluation and will then be exited from the study and no further data or information will be collected on these subjects.

In Phase I, subjects will return to the clinic for monthly visits up to 6 months for post-trial procedures and every three months through the 12-month post-trial visit, and then every six months thereafter until regulatory approval is achieved, estimated to be up to 60 months.

In the first 28 days of Phase II, subjects will receive 2 hours of continuous daily stimulation using the external Wireless Transmitter. At the end of 28 days treatment efficacy will be assessed. Subjects with acceptable efficacy (≥50% reduction in number of UUI episodes) will be considered responders and will continue in post-implant follow-up with 2 hours of daily stimulation using the Wireless Transmitter. Those with less than acceptable efficacy (<50% reduction in number of UUI episodes) will continue for an additional 14-day period with 4 hours of daily stimulation with the Wireless Transmitter. After 14 days of 4 hours of daily stimulation those subjects with ≥50% reduction in number of UUI episodes will be considered a responder. Those subjects who increased to 4 hours of daily stimulation, regardless of responder or non-responder status at the end of the 42-day period will continue in the post-implant follow-up with 4 hours of daily stimulation. A decision to continue a subject with less than a 50% improvement at the end of the 42-day period will be made by the investigator based on what they determine is in the best interest of the subject.

A subject may withdraw their consent from participation at any time regardless of responder status.

Subjects will continue to be followed post-implant for monthly visits up to 6 months and every three months through the 12-month visit, and then every six months thereafter until regulatory approval is achieved, estimated to be up to 36 months.

7.2 Investigational Device and Comparators

This is a single-arm study where subject's baseline assessment is the base comparator. There are no comparator devices.

7.3 Study Sites and Subject Enrollment Limits

The pivotal phase (Phase II) of the study will have up to 35 participating clinical sites in the US, Canada and Europe. Up to 255 subjects will be enrolled across 35 clinical sites. The point of study subject enrollment is when the subject signs the informed consent. The number of implants will be limited to 25 subjects at any one clinical site. Consideration will be given to lifting the 25 subject implanted cap if the investigator makes a request of the sponsor. We expect no more than 5 sites to be included from Europe and Canada. More than 50% of the subjects enrolled will be from the United States.

Clinical sites included in the study will have met study qualification requirements, received necessary institutional review board/ethics committee and/or other approvals, be in countries in which the study is approved as required by law, and be approved by the Sponsor to participate.

Geographies being considered for the study include United States, Canada, and Europe. Additional countries may be considered for participation.

7.4 Subjects

7.4.1 Inclusion Criteria

Subjects must meet all of the following criteria:

General inclusion criteria:

1. Is willing and able to understand and has voluntarily signed and dated the current approved informed consent.
2. Is male or female 22 years of age or older.
3. Has a Body Mass Index (BMI) greater than or equal to 18 and less than or equal to 40 kg/m^2.
4. Is a good surgical candidate and is capable of participating in all testing and follow-up clinic visits associated with this clinical study and is capable of independently using the system components as described in the Patient Manual.
5. Is ambulatory and able to use toilet without assistance.
6. Has a diagnosis of UUI for greater than or equal to 6 months prior to the screening baseline visit date.
7. Has typical residual bladder volume <150 cc tested within 6 months prior to the screening baseline visit date or is willing to have a test at screening baseline visit.
8. Has urodynamic testing (uroflowmetry, cystometry, and pressure flow) completed within 6 months prior to the screening baseline visit date or is willing to have testing at the screening baseline visit.
9. Has cystoscopy testing completed within 6 months prior to the screening baseline visit date or is willing to have a test at the screening baseline visit.
10. Has failed or was not a candidate for more conservative treatment (e.g., pelvic floor exercise, biofeedback, behavioral modification)
11. Has failed, could not tolerate (stopped taking medication due to lack of efficacy or intolerable side effects), or not a good candidate for (as determined by treating physician) at least one (1) antimuscarinic or β_3 adrenoceptor agonist medication.
12. Is willing and able to washout (at least five half-lives) from OAB medications for a period determined appropriate based on type of OAB medication prior to the baseline bladder diary and remain off OAB medications through the 12-month follow-up visit.
13. Has appropriate sacral anatomy as determined by sponsor's and investigator's analysis of radiographic imaging. (The distance from the surface of the skin in the prone and seated position to the bone edge of the S3 foramen must be within the capabilities of the system).

Baseline Bladder Diary Inclusion Criteria:

14. Has a diagnosis of UUI with at least 4 UUI episodes on a 72 - hour diary, and minimum of one (1) UUI episode per 24-hour period.

7.4.2 Exclusion Criteria

Subjects will be excluded if any of the following criteria are met:

General exclusion criteria:

1. Has a hemoglobin A1c of >8%, or has diabetes mellitus with glucosuria.
2. Has diabetic neuropathy.
3. Has interstitial cystitis or bladder pain syndrome as defined by either American Urological Association (AUA) or European Association of Urology (EAU) guidelines, chronic pelvic pain, or recurrent symptomatic urinary tract infections.
4. Has skin, orthopedic, neurological, or hematological (bleeding disorder) or anatomical limitations that could prevent successful placement of the neurostimulator.
5. Has broken, blistered skin or compromised circulation in the area of the neurostimulator implant.
6. Has neurogenic bladder dysfunction such as traumatic or atraumatic myelopathy, multiple sclerosis, Parkinsonism, or history of cerebrovascular accident.
7. Has documented urinary retention within 6 months prior to the screening baseline visit date.
8. Has clinically significant bladder outlet obstruction.
9. Is currently undergoing or has previously undergone pelvic irradiation.
10. Is a subject with a mechanical obstruction such as benign prostatic hypertrophy, urethral stricture, or cancer.
11. Has current grade 3 or 4 pelvic organ prolapse including cystocele, rectocele, enterocele, procidentia, or vaginal vault prolapse.
12. Has symptomatic urinary tract infection (UTI); the subject may be considered for study enrollment if the subject is symptom-free after a full course of treatment prior to beginning the baseline bladder diary. If an asymptomatic bacteriuria is detected during the urinalysis performed at screening, a subject may be enrolled without a waiting period relative to UTI treatment.
13. Has primary stress incontinence or mixed incontinence where the stress component predominates or has been treated surgically for stress urinary incontinence within 6 months prior to the screening baseline visit date.
14. Has received tibial nerve stimulation (TNS) in the past 3 months for the treatment of overactive bladder or unwilling to stay off TNS therapy for 12-month period following implant.
15. Has received treatment of urinary symptoms with any botulinum neurotoxin type-A (BoNT-A) agent in the past 12 months; (e.g. obotulinumtoxinA, Botox®, abobotulinumtoxinA, Dysport®, IncobotulinumtoxinA, Xeomin®).
16. Is a woman who is pregnant or planning to become pregnant during this clinical study or is a woman of child-bearing potential who is not using a medically acceptable method of birth control. Women of child-bearing potential must undergo a pregnancy test, with clear negative result.
17. Has active substance abuse, including alcohol.

18. Has a known hypersensitivity or contraindication to procedural or post-procedural medications which cannot be adequately managed medically.
19. Has a known hypersensitivity to Neuspera's SNS System device components.
20. Has previously failed SNS therapy.
21. Has active implantable medical devices such as neurostimulators, drug pumps, pacemakers, or internal defibrillators since compatibility has not been assessed.
22. Has known needs for diathermy (shortwave, microwave, or therapeutic ultrasound), and radiofrequency ablation in the vicinity of the neurostimulator since these procedures have not been evaluated.
23. Has a known need for therapeutic ultrasound in the area of the sacral nerve neurostimulator as the device can inadvertently concentrate the ultrasound field and cause harm.
24. Has a known need for therapeutic ionizing radiation as can damage the electrical components of the sacral nerve stimulator and any damage may not be immediately detectable.
25. Has plans to enroll or is currently enrolled in another investigational device or drug trial during his/her participation in this study.
26. The investigator is unable to elicit an appropriate motor response in the subject during the intra-operative testing of the implant procedure.

7.4.3 Definition of Enrollment

Phase I: Subjects were considered enrolled in the study after signing the informed consent form and after an implant was attempted. The principal investigator ensured that the subject had met all pre-operative eligibility criteria prior to enrollment in the study. The intraoperative eligibility criterion of an appropriate motor response was confirmed during the implant procedure. Subjects in whom an implant was attempted but the appropriate motor response was not observed, were considered enrolled in the study but did not go on to receive the neurostimulator implant.

Phase II: In compliance with ISO 14155, subjects will be considered enrolled at the time the subject signs and dates the study specific informed consent form. Subjects who do not meet all eligibility criteria are considered enrolled in the study but will not receive an implant. Subjects in whom an implant is attempted but the appropriate motor response is not observed, will be considered enrolled in the study but will not go on to receive the neurostimulator implant.

7.4.4 Subject Withdrawal, Discontinuation, and Study End

Phase I study subjects who were implanted with the Neuspera Implantable SNS System and were determined to be responders during the SNS trial period are being followed in the post-trial period.

Phase II study subjects who are implanted with the Neuspera Implantable SNS System will be followed in the post-implant period.

Subjects who become pregnant during the study will have stimulation stopped for the duration of the pregnancy and will return for follow-up visits.

A subject's participation in the study is voluntary and subjects may choose to exit the clinical trial at any time. Subjects who do not have any part of the Neuspera Implantable SNS System introduced into the body, may be exited from the study immediately. Subjects who have been implanted with the Neuspera SNS System, will have the implanted neurostimulator explanted and complete a 30-day post-explant follow-up prior to study exit. These subjects must return the Patient Controller, Wireless Transmitter(s) and Wireless Transmitter Charging Pad and Magnet to the investigational center. Subject may dispose of used custom undergarments or Wearable at their discretion.

The investigator will document the reason for subject study exit and record the reason, if known, on a study exit form. This information will be recorded for subjects who exit after enrollment and subjects who complete the study. After exit from the study, subjects will be followed per standard of care.

For those subjects who miss a scheduled study visit, the site shall make all attempts at contacting the subject and at a minimum contact must be made three times, with at least one attempt being a certified letter, prior to considering the subject lost to follow-up (LTF).

For subjects who withdraw from the study early, all attempts will be made to collect the primary and secondary endpoint data, including safety data.

A subject's continued participation in the study may be terminated for the following reasons:

- Serious or severe adverse event or unanticipated adverse device effect.
- Termination of study by the Sponsor.
- Investigator determines that continued participation is not in the best interest of the subject.
- Pregnancy
- Subject withdrawal of consent at any time.

Enrollment will stop when 120 subjects have had attempted implants. At that time, if there are subjects enrolled, but not yet implanted, they may continue in the study and receive an implant.

7.4.5 Subject Replacement

Subjects will be enrolled once into the study and cannot be enrolled again. The sample size calculations have accounted for subject lost to follow-up, thus subjects who exit after enrollment will not be replaced. Additionally, subjects who fail screening, will not be re-screened at a later time.

7.5 Procedures

7.5.1 Screening/Baseline

Potential study subjects will be identified and informed of the study. Subjects who provide informed consent for study participation will undergo baseline screening evaluations to determine their eligibility for study participation. These evaluations will be done at the Screening/Baseline visit and include:

- Inclusion/Exclusion review
- Demographics
- Medical history
- OAB history
- Medication Use (includes OAB medications and therapies)
- Physical examination
- Vital Signs
- Hemoglobin A1c collection
- Urinalysis
- Pregnancy test (as applicable)
- A radiographic image (X-ray or fluoroscopy) to determine sacral thickness to provide the recommended model (SNS-28 or SNS-35) for implant. For sacral thickness of 16.5 mm or less the SNS-28 neurostimulator is recommended for implant and for sacral thickness >16.5 mm, the SNS-35 is recommended for implant. The final device model implanted will be based on the investigator's assessment at the time of implant.
- A radiographic image (X-ray or fluoroscopy) assessment of the distance from the skin surface to the bone edge of the S3 foramen on all subjects. The X-ray image can be the same image as the image taken to determine sacral thickness.
- Urodynamics (uroflowmetry, cystometry, and pressure flow). Completed within 6 months of screening/baseline visit or test at the screening/baseline visit.
- Cystoscopy completed within 6 months of screening baseline visit or at screening/baseline visit.

7.5.2 Informed Consent

Prior to any study related procedures, the investigator or delegated staff must explain the study, answer any questions the subject may have, and provide the subject with the approved consent form to read. The informed consent form must be approved by the reviewing IRB/EC.

In order to participate in the study, the subject must sign and date the informed consent form.

All applicable laws, regulations, and IRB/EC requirements must be followed during the consent process.

7.5.3 OAB Medication Washout and Therapy Discontinuation

Standard medications and therapies used for OAB should be stopped before the scheduled Neuspera Implantable SNS System procedure. These medications, and therapies, must be stopped for a period of at least five half-lives before the baseline bladder diary is completed. For a given subject, the drug they are on with the longest half-life (X5) will determine the length of the washout period. Subjects will remain off these OAB medications through the 12-month post-trial period for Phase I and Phase II.

7.5.4 Custom Undergarments

Subject's normally worn undergarment size will be recorded. Custom undergarments will be provided to the subject in the same size that they normally wear. Subject will be asked to wear the custom undergarments and to inform the research staff if an alternate size (smaller or larger) will be required. The subject will be provided with the size that best fits them prior to or at the implant visit. New undergarments will be provided if needed if body size changes over time.

7.5.5 Wearable

Subjects can elect to use the Wearable or the custom undergarment to hold the WT in place. At any time during the study, the subject can use either the custom undergarment or the Wearable.

7.5.6 Baseline Assessments

It is acceptable to complete OAB washout and subsequent Baseline Assessments prior to Urodynamic, Cystoscopy procedures, and Assessment of Sacral Anatomy. This would ensure subjects meet the primary criteria for UUI before undergoing invasive procedures.

7.5.6.1 Assessment of Sacral Anatomy

A radiographic image (x-ray or fluoroscopy) must be completed to determine sacral thickness and the distance from the skin surface to the bone edge of the S3 foramen on all subjects.

7.5.6.2 Bladder Diary

Subjects must complete a baseline 72-hour bladder diary to confirm inclusion and exclusion criteria. The baseline 72-hour bladder diary must be completed when the potential subject has been off OAB medications for a period determined appropriate based on type of OAB medication (at least five half-lives). The following inclusion criterion must be confirmed prior to the Neuspera implant procedure:

- Has a diagnosis of UUI with at least 4 UUI episodes on a 72-hour diary, and minimum of one (1) UUI episode per 24-hour period.
- Subjects must remain off OAB medications through the 12-month post-trial period for Phase I and post-implant for Phase II.

7.5.6.3 Wexner Scale (Fecal Incontinence Assessment)

Subject must complete the Wexner Scale after they have been off OAB medications for a period determined appropriate based on type of OAB medication (at least five half-lives). The Wexner scale will only be completed by subjects who have FI concomitant with UUI at baseline as documented in the baseline medical history.

7.5.6.4 Quality of Life Measures

Subject must complete the health-related quality of life questionnaires (ICIQ-OABqol and MLUTS/FLUTS) after they have been off OAB medications for a period determined appropriate based on type of OAB medication.

7.5.6.5 Physician Review Panel

A member of the physician review panel, experienced in the implant of sacral neuromodulation devices, will review all inclusion / exclusion criteria and associated medical history for subjects prior to approving subjects for implant in the trial.

7.5.6.6 Sacral Nerve Stimulation (SNS) Pre-Implant Assessments

Pre-implant assessments include:

- Inclusion/Exclusion review
- Vital Signs
- Adverse Events
- Changes to medication (including OAB medications) and OAB therapies

7.5.7 Implant Procedure

The implant procedure will be scheduled with the goal to be completed within six weeks following the date of subject informed consent. If additional time is required to accommodate participants and surgical schedules, procedures can occur after six weeks from informed consent but no later than 12 weeks following the completion of the baseline 72-hour bladder diary. If scheduled beyond 12 weeks, the 72-hour baseline bladder diary will need to be repeated following washout of any OAB medications that may have been restarted. Prior to proceeding with the implant procedure, the investigator will review and confirm inclusion and exclusion criteria. One exception is the exclusion criterion related to the failure to elicit an appropriate motor response during the intra-operative testing of the implant procedure as this cannot be confirmed until the implant procedure is attempted.

The implant procedure will be performed in accordance with approved Neuspera Implantable Sacral Nerve Stimulator Kit Instructions for Use and Neuspera Intraoperative Kit Instructions for Use.

The subject will be prepped and will undergo local anesthesia, intravenous conscious sedation or general anesthesia. The S3 foramen will be located per Neuspera's Implantable Sacral Nerve Stimulator Kit Instructions for Use. Following appropriate identification of the sacral nerve, the neurostimulator will be implanted and a stimulation threshold will be confirmed by noting motor responses of anal bellows and/or flexion of the big toe or movement in other toes. If motor responses are not observed in the S3 foramen or if the physician assesses that better motor response may be achieved in the contralateral S3 foramen or the S4 foramen, then the placement may be attempted at these locations, following a similar procedure used to identify the sacral nerve location in the S3 foramen. Following implantation of the neurostimulator, motor responses will be observed for each of three electrode pairs. The goal is to have motor response for all three electrode pairs. If motor responses are not observed for each electrode pair, the physician may remove the device, re-thread it, and re-implant, and retest for motor responses in a new location. This can be done up to two more times with a specific neurostimulator. If more attempts are needed, a new neurostimulator must be used. If after multiple attempts to position a device in the same, contralateral, or S4 foramen are unable to yield three electrode pairs with motor responses, two out of three electrode pairs is acceptable. If the physician determines suitable motor response cannot be achieved, the device should not be implanted. After confirming the stimulation thresholds for all electrode pairs, a neurostimulator position confirmation radiographic image will be completed, and the tethering suture will be clipped, and the incision closed in accordance with approved Neuspera's Implantable Sacral Nerve Stimulator Kit Instructions for Use. A bandage will be placed over the incision site.

If the device is a replacement device, the device may be replaced at the time it is determined a replacement is necessary. As the subject has already been enrolled in the study, the inclusion and exclusion criteria list will not be reviewed again prior to a device replacement.

7.5.7.1 SNS Post-operative Care

The subject's post-operative care will be per the institution's standard medical practice. In addition, subjects will be instructed to follow guidelines on activities for six weeks following the implant procedure. Subjects will be informed to avoid sexual activity during the first week following the implant of the neurostimulator. Subjects will be instructed to limit physical activities that may put stress on the implanted device. Activities that include sudden, excessive, or repetitive bending, twisting, bouncing, or stretching can cause component fracture or dislodgement. Component fracture or dislodgement may result in loss of stimulation, intermittent stimulation, stimulation at the fracture site, and additional surgery to replace or reposition the component. Examples of such activities include gymnastics, mountain biking, and other sports or equipment that involve the movements described above. Strenuous physical activity may cause implant fracture or dislodgement which may result in loss of stimulation, intermittent stimulation, or pain at the implant site. Postural changes, and other activities may result in the subject perceiving an increase in stimulation which may be uncomfortable. Some subjects have described this as a jolting or shocking sensation. Subjects should be instructed to not wear the Wireless Transmitter to deliver therapy during activities that could be unsafe for themselves or others (e.g, driving or the use of dangerous equipment) if they were to receive an unexpected jolt or shock. Instruct subjects to consider movements involved in any planned activity and take precaution to avoid putting undue stress on the implanted system. For example, in activities such as skydiving, when the parachute opens, there can be a sudden jerking motion that occurs. This may cause a neurostimulator dislodgement or fracture. A surgical procedure may be required to reposition or replace the neurostimulator.

Subjects will be asked to inform the investigator about the activities in which they participate to determine if there should be any additional restrictions.

Subjects will also be instructed for the duration of study participation to refrain from receiving any form of spinal or pelvic manipulation in the area of the neurostimulator by chiropractors as this may damage the implant. This may result in implant fracture or dislodgement which may result in loss of stimulation, intermittent stimulation, or pain at the implant site. Subjects will also be asked to refrain from manipulating the implant. Pushing on or rubbing the implant site may cause implant damage, dislodgement, uncomfortable stimulation, or pain at the implant site.

Pre-discharge data collection will be completed and include the following assessments:

- Vital Signs
- Adverse Events
- Wound Check
- Wireless Transmitter positional testing
- Record Device Parameters

Follow the 'Post-Operative Patient Training and Follow-up Instructions' provided in the Clinician Manual for training the subject on system use and programming stimulation settings. The Neuspera system will be programmed in accordance with the Clinician Manual. During the study, sensory threshold responses with different electrode configurations and RF Power level adjustment of the Wireless Transmitter will be made.

Subjects will follow instructions provided by the investigator and study staff, along with the Patient Manual. Subjects will wear the Wireless Transmitter to receive therapy delivery per the Investigator's directions (2 hours continuously per day) during the SNS trial period in Phase I and post-implant period in Phase II. Subjects will be encouraged to wear the Wireless Transmitter during a consistent time each day, e.g., 6 am to 8 am, or 7 pm to 9 pm, etc.

7.5.8 SNS Follow-up Visits

The research coordinator will call the subject 1-3 days post implant to ensure the subject understands all post implant training requirements on the use of the system including:

- Proper charging of the Wireless Transmitter on the Charging Pad
- Proper use of the Magnet with the Wireless Transmitter
- Placement of the Wireless Transmitter in the undergarment or Wearable for 2 hours of continuous stimulation per day
- Proper use of the stimulation diary
- Proper use of the Patient Controller to adjust stimulation amplitude or programs.

The research coordinator will provide re-training as appropriate.

7.5.8.1 Phase I

The enrollment and trialing phase has been completed for Phase I of the trial. The trialing phase visit schedule will remain in the protocol until all subjects complete 3-months of follow-up.

Subjects are required to return to the clinic 7-days, 14-days and 21-days post procedure during the Phase I SNS trial period. Just prior to each of these clinic visits, subjects will complete a 72-hour bladder diary documenting the number of voids, voided volume (specified times), leaks, urgency episodes (leaks and voids), and pad use. During the Therapy Session, when the subject is wearing the Wireless Transmitter and receiving stimulation therapy, the subject must also complete a Stimulation Diary noting stimulation sensation approximately every 30 minutes. If the subjects do not feel the stimulation during the stimulation sensation checks, they are instructed to adjust the undergarment or Wearable, increase the stimulation amplitude, or change programs until they feel a comfortable level of stimulation. Subjects should repeat this process every 30 minutes, each hour or every 2 hours depending on what duration of daily stimulation is being used. At the end of the therapy session subjects will be asked to answer questions on the diary about that session regarding the consistency of stimulation. The overall goal is that subjects feel a comfortable level of stimulation throughout the stimulation period.

The following will be completed and documented during the SNS trial period follow-up visits:

- Review of subject therapy and usage history

- Device data will be periodically recorded.
- Adjustments of device stimulation parameters on Clinician Programmer
- Vital Signs
- Changes to medication (including OAB medications) and OAB therapies
- Adverse event assessment
- Wound check
- 72-hour bladder diary (reviewed)
- Stimulation Diary (reviewed)
- Pain Questionnaire (Day 7 only)
- Wexner Scale (reviewed, only in subjects with FI at baseline)

Subject's completed 72-hour bladder diary will be reviewed and SNS therapy response will be determined. A responder is defined as a subject who experiences at least a 50% improvement in the number of UUI episodes from baseline.

If the investigator determines that SNS therapy is a treatment option for the subject, the subject will continue to participate in the post-trial follow-up period of the clinical study and will have the post-trial procedures.

If the investigator determines that the subject did not respond to SNS therapy with 2 hours of daily stimulation, the subject will continue with an additional 14 days of trial with 4 hours of continuous daily stimulation. During the Therapy Session, when the subject is wearing the Wireless Transmitter and receiving stimulation therapy, the subject must also complete a Stimulation Diary noting stimulation sensation approximately every hour during the 4-hour therapy session. If the subjects do not feel the stimulation during the stimulation sensation checks, they are instructed to adjust the undergarment or Wearable, increase the stimulation amplitude or to change programs until they feel a comfortable level of stimulation. Subjects should repeat this process every hour, if needed, to feel a comfortable level of stimulation. The overall goal is that subjects feel a comfortable level of stimulation throughout the 4-hour stimulation period.

The subject will return to the clinic at approximately 28- and 35-days post-implant procedure. At the 35-day visit the physician will determine if the subject is a responder, i.e., has ≥50% reduction in the number of UUI episodes from baseline. If the subject is determined a responder, the subject will continue to participate in the post-trial period and will have the post-trial procedures. The subject will continue in the post-trial period with 4 hours of daily stimulation therapy.

If the investigator determines the subject has <50% reduction in the number of UUI episodes from baseline, the subject will continue in the trial period for an additional 14 days with 8 hours of continuous daily therapy stimulation. During the Therapy Session, when the subject is wearing the Wireless Transmitter and receiving stimulation therapy, the subject must also complete a Stimulation Diary noting stimulation sensation approximately every 2 hours during the 8-hour therapy session. If the subjects do not feel the stimulation during the stimulation sensation checks, they are instructed to adjust the undergarment or Wearable, increase the stimulation amplitude, or change programs until they feel a

comfortable level of stimulation. Subjects should repeat this process every 2-hours, if needed, to feel a comfortable level of stimulation. The overall goal is that subjects feel a comfortable level of stimulation throughout the 8-hour stimulation period.

The subject will return to the clinic at approximately 42- and 49-days post-implant procedure. The investigator will determine at approximately 49 days if the subject is a responder. If the subject is determined to be a responder with ≥50% reduction in the number of UUI episodes from baseline, the subject will continue to participate in the post-trial period and will have the post-trial period procedures completed. The subject will continue in the post-trial period with 8 hours of daily stimulation therapy.

At the end of the trial period, if 8 hours of daily stimulation therapy did not provide a ≥50% reduction in the number of UUI episodes, the subject is considered a non-responder to SNS therapy. The subject may discuss alternative therapy options with the investigator to determine if the neurostimulator will be removed. Subjects may remain in the trial at 8 hours of continuous stimulation. If the subject and the investigator determine that it will be in the subject's best interest the neurostimulator may be removed. The neurostimulator will be explanted and alternative therapy options will be discussed with the subject by the investigator. The Wireless Transmitter(s), Wireless Transmitter Charging Pad, Magnet and Patient Controller will be returned to the investigational center. Subjects may dispose of used custom undergarments or Wearable at their discretion. These subjects will be followed for 30-days for safety following the post-trial period and will then be exited from the study and no further data or information will be collected on these subjects.

7.5.8.2 Phase II

The implant procedure and post procedure care in Phase II is consistent with that performed in Phase I. In the first 28 days post implant, subjects will receive 2 hours of continuous daily stimulation using the external Wireless Transmitter. At the end of 28 days treatment efficacy will be assessed. Subjects with acceptable efficacy (≥50% reduction in number of UUI episodes) will be considered a responder and will continue in the post-implant follow-up with 2 hours of daily stimulation using the Wireless Transmitter. Those with less than acceptable efficacy (<50% reduction in number of UUI episodes) will continue for an additional 14-day period with 4 hours of daily stimulation with the Wireless Transmitter. After 14 days of 4 hours of daily stimulation those subjects with ≥50% reduction in number of UUI episodes will be considered a responder. Those subjects who increased to 4 hours of daily stimulation, regardless of responder or non-responder status at the end of the 42-day period will continue in the post-implant follow-up with 4 hours of daily stimulation. A decision to continue a subject with less than a 50% improvement at the end of the 42-day period will be made by the investigator based on what they determine is in the best interest of the subject.

The following will be completed and documented using the appropriate CRFs during the post-implant follow-up visits:

- Review of subject therapy and usage history
- Device data will be periodically recorded
- Adjustments of device stimulation parameters on Clinician Programmer
- Vital Signs
- Changes to medication (including OAB medications) and OAB therapies

- Adverse event assessment
- Wound check
- 72- hour bladder diary (reviewed)
- Stimulation Diary (reviewed)
- Wexner Scale (reviewed, only in subjects with FI at baseline)

During the post-implant period, subjects will complete a 72-hour bladder diary documenting the number of voids, voided volume (specified times), leaks, urgency episodes (leaks and voids), and pad use prior to each clinic visit.

During the Therapy Session, when the subject is wearing the Wireless Transmitter and receiving stimulation therapy, the overall goal is to feel a comfortable level of stimulation. Subjects must complete a Stimulation Dairy to document daily therapy use.

Subject's completed 72-hour bladder diary will be reviewed and SNS therapy response will be determined. A responder is defined as a subject who experiences a ≥50% reduction in the number of UUI episodes from baseline. At the day 28 or day 42 clinic visit post-implant the responder rate will be determined. As an as-treated mITT analysis will be completed, all implanted subjects will continue in the post-implant follow-up period regardless of responder rate outcome.

7.5.8.3 Phase I Post-Trial Procedure Final Visit

The enrollment and trialing phase has been completed for Phase I of the trial. The end of trialing phase visit schedule will remain in the protocol until all subjects complete 3-months of follow-up.

Phase I subjects determined to be SNS responders at the end of the trial period (either day 21, day 35, or day 49) will have a post-trial procedure final visit. The following procedures will be completed at this visit:

- Wound check
- Neurostimulator position confirmation lateral and anterior/posterior radiographic image
- Subject User Experience Questionnaire

Phase I subjects will have the post-trial procedures occur at the trial visit at which they were determined to be a SNS responder (either the 21-day, 35-day, or 49-day visit). A wound check will be completed, and radiographic images will be taken to confirm position of the neurostimulator. Follow-up visits will occur from the last trial visit, for example, if the last trial visit was at the 21-day visit, the one-month follow-up will be one month from the 21-day visit. Instructions will be provided on the daily stimulation requirement for the post-trial follow-up.

7.5.8.4 Phase II Responder Rate Assessment (Day 28 or Day 42 Clinic Visit)

At the Day 28 or Day 42 clinic visit post-implant the responder rate will be determined. This responder rate will be used for comparison to current clinical literature. Subjects determined to be responders and those determined to be non-responders will continue in the study. A decision to continue a subject with

less than a 50% improvement at the end of the 42-day period will be made by the investigator based on what they determine is in the best interest of the subject.

The following procedures will be completed at the Day 28 or Day 42 clinic visit post-implant:

- Wound check
- Neurostimulator position confirmation lateral and anterior/posterior radiographic image
- Subject User Experience Questionnaire

Phase II subjects will have a wound check completed, and radiographic images taken to confirm position of the neurostimulator at the time the subject is determined to be a responder or non-responder post-implant (day 28 or day 42 clinic visit). Investigators will make an assessment of the radiographic image to determine if any movement of the device has occurred. The CEC will review all images to determine if movement has occurred, and any disagreement between the CEC and the investigator will be reviewed by the DSMB, who will make the final decision.

All follow-up visits will occur from date of implant, for example, the Month 6 visit is six months from the date the device was implanted. Instructions will be provided on the daily stimulation requirement for the remainder of the post-implant follow-up.

7.5.8.5 Follow-up Clinic Visits

Phase I: Only subjects determined to be responders will complete follow-up clinic visits.

Phase II: All subjects, responders and non-responders, will complete follow-up clinic visits.

Subjects enrolled in Phase I and II will return to the clinic for monthly visits up to the 6-month post-trial (Phase I) and the 6-month post-implant (Phase II) procedure. After the 6-month visit, clinic visits will occur every three months up through the 12-month visit, and then every 6 months until regulatory approval is achieved.

The following will be completed and documented using the appropriate CRFs during the follow-up visits:

- Review of subject therapy and usage history
- Device data will be periodically recorded.
- Adjustments of device stimulation parameters on Clinician Programmer
- Vital Signs
- Body Weight assessment (at 12, 24, 36 month visits only – and 42 and 60 month for Phase I).
- Changes to medication (including OAB medications) and OAB therapies
- Adverse event assessment
- 72-hour bladder diary (reviewed)
- Stimulation Diary (reviewed)
- Wexner Scale (reviewed, only in subjects with FI at baseline)
- Health-related quality of life questionnaires (ICIQ-OABqol, MLUTS/FLUTS) as listed in Table 7 (Phase I) and Table 9 (Phase II).
- PGI-I as listed in Table 7 (Phase I) and Table 9 (Phase II).

- Subject User Experience Questionnaire as listed in Table 7 (Phase I) and Table 9 (Phase II).

7.5.8.6 Follow-up Telephone Visits

Phase I: Only subjects determined to be responders will complete follow-up telephone visits.

Phase II: All subjects, responders, and non-responders, will complete one scheduled follow-up telephone visit at 5.5 months. Unscheduled telephone visits can be made to check on subject status.

The following will be completed and documented in electronic data capture (EDC) for Telephone Visits:

- Changes to medication (including OAB medications) and OAB therapies
- Adverse event assessment
- Stimulation Diary (reviewed)

7.5.8.7 Programming Sessions

During follow-up visits, subjects will bring their Wireless Transmitter for interrogation and data transfer to the Clinician Programmer. Subjects may be asked to bring their Charging Pads to the follow-up visits for retraining purposes.

Data from the Wireless Transmitter will be periodically downloaded on subject therapy and usage. Device programs will be reviewed and adjusted per Investigator discretion.

Programming adjustments may occur as many times as needed during the study to optimize treatment. Programming will be performed in accordance with the Clinician Manual.

7.5.8.8 Unscheduled Follow-Up Visits in the Clinic or via Telephone

If a subject is seen for an unscheduled visit the following will be completed and documented in the EDC.

- Changes to medication (including OAB medications) and OAB therapies
- Adverse event assessment

If the reason for the unscheduled visit is due to troubleshooting loss of efficacy or painful stimulation, the subject may be asked to complete the following procedures in addition to the above listed procedures.

- 72-hour bladder diary within 7 days. Voided volume not needed on diary.
- Radiographic imaging of the implanted device
- Device Parameter/Download
- Adjustments of device stimulation parameters on Clinician Programmer

7.5.8.9 Device Replacements

During the course of the study, subjects may require a replacement of the neurostimulator. If a subject receives a neurostimulator replacement prior to Month 3 clinic visit in Phase I, the subject will repeat trialing and follow-up, as the newly replaced device may not be in the identical location as the previous device (i.e., new location on ipsilateral side, contralateral side or different foramen). If a subject receives a device replacement prior to Month 6 clinic visit in Phase II, the subject will repeat all post-implant

procedures including the Day 28 and Day 42 (if needed) response rate assessment and follow-up visits. Both in Phase I and Phase II, the date of replacement will be considered the new device implant date for analysis and follow-up purposes. Subjects with device replacement will begin with procedures listed in Section 7.5.6.6 (Sacral Nerve Stimulation Pre-Implant Assessments), with the exception of the inclusion/exclusion checklist, and continue in the study as outlined following an implant for Phase I or Phase II, as appropriate. If a device replacement is required after the time periods indicated above (Month 3, Phase I; Month 6, Phase II), subjects will be managed as determined best by the investigator to obtain optimal programming settings, that is, no trialing (Phase I) and no response rate assessment (Phase II). Subjects will continue on their original follow-up schedule without repeating any of the assessments or follow-up visits already completed.

The following data will be collected for device replacements:

- Reason for device replacement
- Device Parameter/Download (prior to device explant)
- Replacement/explant procedure data
- Fluoroscopy images for replacement
- Vital Signs
- Changes to medication (including OAB medications) and OAB therapies
- Adverse event assessment (any signs or symptoms associated with the reason for replacement, will be reported as an adverse event)

The explanted neurostimulator should be placed in a biohazard kit and shipped to the Sponsor for investigation. The neurostimulator must be handled carefully and as little as possible to prevent damage and preserve its integrity. The Sponsor must be contacted for shipping and packaging materials and to arrange for transport.

7.5.8.10 Device Explants

At study exit or during the course of the study, subjects may require a neurostimulator explant. The subject will be prepped according to local practice. A small incision (approximately 2.5 cm) will be made at the site of implantation and the tether will be located. The device will be removed by pulling the tether in the direction of the implantation path. If the device cannot be completely removed using the tether, the investigator will locate the top of the implant by palpating or using fluoroscopy. The investigator will retrieve the device using forceps to grip the top of the implant. The wound site will be closed, and the subject will proceed to post-procedure recovery. Post-recovery procedures will be according to local practice. The following data will be collected for explants:

- Reason for device explant
- Device Parameter/Download (prior to device explant)
- Explant procedure data
- Fluoroscopy images prior to device explant
- Vital Signs
- Changes to medication (including OAB medications) and OAB therapies

- Adverse event assessment (any signs or symptoms associated with the reason for explant, will be reported as an adverse event)

Subjects will return the Wireless Transmitter(s), Wireless Transmitter Charging Pad, Magnet and Patient Controller to the investigational center. Following explant, the neurostimulator should be placed in a biohazard kit and shipped to the Sponsor for investigation. The neurostimulator must be handled carefully and as little as possible to prevent damage and preserve its integrity. Subjects may dispose of used custom undergarments or Wearable at their discretion. The Sponsor must be contacted for shipping and packaging materials and to arrange for transport.

All relevant data pertaining to the explant must be documented and supporting documentation (i.e., radiographic images and photographs) will be made available to the sponsor.

7.5.8.11 Post-Explant 30-Day Follow-up

A 30-day follow-up visit is required for all subjects where the implant procedure was attempted but the device was not implanted or where the device was explanted. The following measures are required:

- Vitals signs
- Changes to medication (including OAB medications) and OAB therapies
- Adverse event assessment
- Wound check

7.5.8.12 Device Programming and Wireless Transmitter Positional Testing

The Neuspera system will be programmed in accordance with the Clinician Manual. Additionally, the following testing will occur at therapy initiation and as needed, during trial visits, post-trial and post-implant follow-up visits, and unscheduled visits:

- Sensory threshold responses with different electrode configurations.
- RF Power level adjustment of Wireless Transmitter.

7.5.8.13 Troubleshooting Loss of Efficacy or Painful Stimulation

In the event of loss of efficacy or painful stimulation a troubleshooting guidance flowchart has been prepared in Figure 17 below. This troubleshooting guidance is based on established International Continence Society best practice for use of sacral neuromodulation.[10] The guidance is a stepwise assessment starting with medical assessment of the subject, assessment of device function, reprogramming and follow-up and radiographic assessment, if indicated. The investigator will lead care and management of each subject while Neuspera may provide device technical support.

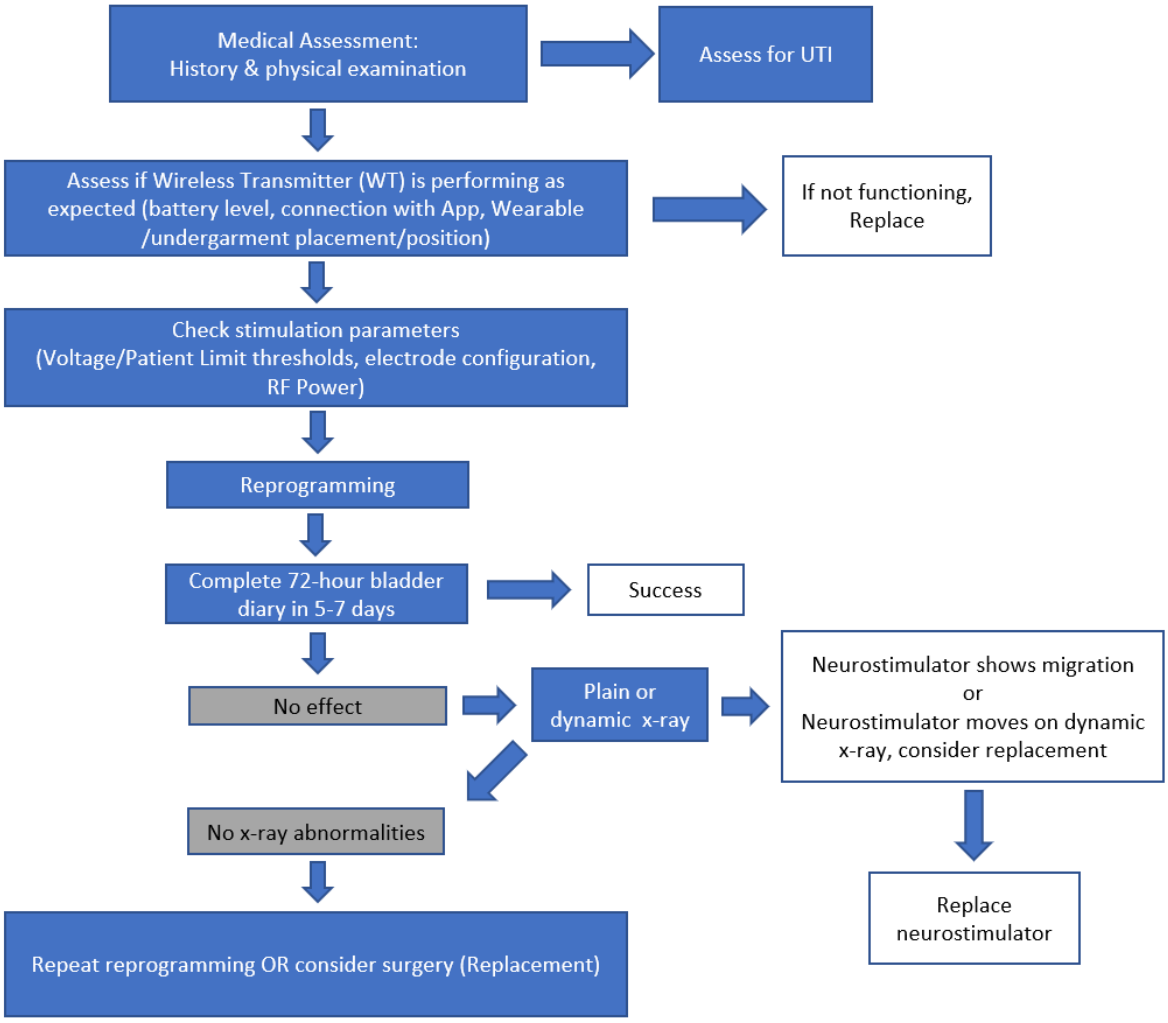


FIGURE 17: TROUBLESHOOTING GUIDANCE FOR LOSS OF EFFICACY OR PAINFUL STIMULATION

7.5.8.14 Magnetic Resonance Imaging (if required for subject)

Non-clinical testing has demonstrated that the neurostimulator is MR Conditional and subjects with the implanted device may be safely scanned in an MR system meeting the conditions described in the Clinician Manual. All external components must be removed before scanning. If a subject has an MR scan while in the study, the following information will be collected:

- Date of MR scan.
- Anatomical location of scan.
- Strength of scan (Tesla).
- Reason for the scan.
- MRI image and information describing any artifacts by the radiologist.

7.5.8.15 Collection of Economic Data

The FDA has assigned Category B (non-experimental / investigational device) for the clinical trial. The Center for Medicare and Medicaid Services (CMS) may pay for the Category B IDE device and routine care items and services furnished in an FDA-approved Category B IDE study if CMS determines that the Medicare coverage IDE study criteria is met.

Once Neuspera obtains CMS coverage for the clinical trial, economic information may be gathered during the trial.

A subset of Medicare beneficiaries (subjects 65 years of age or older) was enrolled in Phase I of the SANS-UUI trial. This group of subjects composed 44% (15/34) of the implanted population. Safety and efficacy data from the subjects implanted demonstrated results similar to the overall study population.

7.5.9 Study Assessments

7.5.9.1 History and Physical Examination

At baseline, a standard physical examination and complete medical history must be taken including co-morbidities and co-existing medical conditions. This includes UUI and genitourinary history.

7.5.9.2 Vital Signs

Clinical status including vital signs must be evaluated and documented at baseline and all follow-up visits. Vital signs include heart rate, respiratory rate, blood pressure and temperature.

7.5.9.3 Questionnaires

Subjects will enter data on an electronic patient reported outcome (ePRO) system.

7.5.9.3.1 Wexner Scale (Fecal Incontinence Assessment)

The Wexner scale assesses the frequency and severity of FI. The score takes into account the type and frequency of incontinence and the extent to which it alters the subject's life. The Wexner scale will only be completed by subjects who have FI concomitant with UUI at baseline.

7.5.9.3.2 ICIQ-OAB

The ICIQ-OAB is a robust, subject-completed questionnaire for evaluating quality of life (QoL) in subjects with overactive bladder, for use in research and clinical practice. The questionnaire explores in detail the

impact on subject's lives of overactive bladder and can be used as an outcome measure to assess impact of different treatment modalities. The questionnaire consists of 26 questions answered by the subject.

7.5.9.3.3 ICIQ-Male/Female Lower Urinary Tract Symptoms

The ICIQ-MLUTS and ICIQ-FLUTS is a subject-completed questionnaire evaluating male and female lower urinary tract symptoms in research and clinical practice. This questionnaire helps to obtain a brief yet comprehensive summary of the impact of urinary symptoms. It also helps to facilitate subject-clinician discussions and assess outcomes from various treatment modalities. The ICIQ-MLUTS consists of 13 questions and ICIQ-FLUTS consists of 12 questions.

7.5.9.3.4 Patient Global Impression of Improvement (PGI-I)

The PGI-I is a subject-completed transition scale that is a single question asking the subject to rate their urinary tract condition now, as compared with how it was prior to beginning treatment on a 7-point scale.

7.5.9.3.5 Subject User Questionnaire

Enrolled subjects will complete a subjective questionnaire. This questionnaire will collect data on the use of, and satisfaction with the Neuspera Implantable SNS System.

7.5.9.3.6 Physician User Experience Questionnaire

The investigator (or a delegated implanting sub-investigator) will complete a subjective questionnaire. This questionnaire will collect data on the use of and satisfaction with the Neuspera Implantable SNS System.

7.5.9.4 Bladder Diary

Subjects will complete 72-hour bladder diaries at the required timeframes. The bladder diary is expected to be completed electronically but paper may be used as a backup.

The 72-hour bladder diary will collect voiding frequency (voids), void volume (specified times), urgency, urinary urgency incontinence (UUI) episodes (leaks), activity during UUI (at baseline only), and pad use. Subjects will record events for a consecutive 72-hour period, starting from when they first begin recording events.

Subjects will be trained on proper methods for completing the diary, collecting, and measuring the urine volume, and distinguishing between urge and stress incontinence episodes.

Baseline Bladder Diary: A baseline 72-hour bladder diary will be completed after the subject has stopped OAB medication for period determined appropriate based on type of OAB medication (at least five half-lives) to confirm the UUI inclusion criterion. At the discretion of the investigator, subjects who failed to accurately complete their diary may be allowed to repeat the diary evaluation. Those who failed to qualify after a second diary attempt will be withdrawn from further study participation.

Follow-up Bladder Diaries: Subjects will complete a 72-hour bladder diary prior to each scheduled clinic visit. Voided volume will only be collected at baseline and at Month 6 and 12 clinic visits. The bladder diary will be completed for a consecutive 72-hour period starting 4-7 days prior to each required follow-up visit. If a subject fails to complete the diary before the scheduled visit date, they may start the 72-

hour diary within 24-hours of the scheduled visit date. If a subject continues to miss the start of the 72-hour diary completion prior to a scheduled visit date, they will be assessed for protocol non-compliance.

If a subject is symptomatic with a UTI prior to beginning or in the middle of a 72-hour bladder diary, it is recommended to the subject start the diary after the subject is asymptomatic after standard-of-care treatment.

Subjects may be requested to complete an additional diary following programming changes to assess the impact of the changes. Subjects completing additional diaries will not need to collect void volume.

7.5.9.5 Stimulation Diary

Enrolled subjects in Phase I and Phase II who receive the Neuspera SNS neurostimulator will complete a stimulation diary during follow-up. Subjects will complete a daily stimulation diary for the first 12 months and a weekly stimulation diary after 12 months. The stimulation diary is expected to be completed electronically but paper may be used as a backup.

Through Month 12 Visit (≤12 Months)

In the first 12 months of therapy subjects will document daily start and stop time of stimulation/therapy session and stimulation sensation. At the end of the therapy session subjects will be asked to answer questions on the diary about that session regarding the consistency of stimulation and how difficult it was to achieve consistent stimulation.

Following 12 Month Visit (> 12 Months)

After the subject has completed their 12-month follow-up visit, they will be required to complete a weekly stimulation diary. The weekly diary will collect how many days the subject used their system in the past week and the average duration of therapy.

The overall goal at each stimulation/therapy session is that subjects feel a comfortable level of stimulation throughout the stimulation period. Subjects will be encouraged to contact the study coordinator if they are having difficulty with the therapy sessions and/or log their difficulty on their stimulation diary. Instructions on completion of the stimulation diary will be reviewed with subjects to ensure understanding of completion requirements.

7.5.9.6 Medications

All current medication subjects are using will be documented at the screening baseline visit. Any changes to medications will be recorded at each subsequent study visit until study exit. Additionally, current and historical OAB and incontinence medications will be reviewed and documented. Subjects must remain off OAB medications for a period determined appropriate based on type of OAB medication (at least five half-lives) prior to completion of the baseline voiding diary and through 12-months post-trial period.

7.5.9.7 Conservative OAB Therapy Log

All current OAB therapies subjects are using will be documented at the screening baseline visit. Any changes to OAB therapies will be recorded at each subsequent study visit until study exit (Phase I) and 12-months post-implant (Phase II).

7.5.9.8 Clinical Laboratory Tests

The following tests will be completed during Screening/Baseline. All blood and urine samples will be disposed of after test is performed.

Hemoglobin A1c (HbA1c): HbA1c will be measured for all subjects, regardless of if they have a history of diabetes, to assess and document exclusion criterion for uncontrolled diabetes.

Urinalysis: A urinalysis will be completed with culture if indicated to assess and document the exclusion criterion of urinary tract infection.

Pregnancy Test: A blood or urine pregnancy test will be completed if subject is a female of childbearing potential and it will be used to assess and document the exclusion criterion for pregnancy.

7.5.9.9 Urodynamics Testing

Subjects must have urodynamics testing to assess study eligibility. Tests performed within 6 months of the subject's screening baseline visit date are acceptable or a test may be conducted at the screening baseline visit. The following tests are required:

Uroflowmetry: Uroflowmetry will be used to assess and document inclusion criterion for Post-Void Residual Volume (PVR), absence of obstruction, and to confirm symptoms of UUI.

Cystometry: Cystometry will be used to assess and document exclusion criterion for neurogenic bladder syndrome.

Pressure Flow: Pressure flow study will be used to assess and document exclusion criterion for bladder obstruction.

7.5.9.10 Assessment of Subject's Sacral Anatomy

A radiographic image (X-ray or fluoroscopy) must be obtained to determine sacral thickness and the distance from the skin surface to the bone edge of the S3 foramen on all subjects.

For the distance from the sacral foramen to the surface of the skin, two images will be obtained:

1. Prone position (similar to how subject would be during implant procedure)
2. Seated position (to estimate sacral depth while seated, using the therapy)

Measurements may be completed by investigational site personal, a radiologist or by Neuspera.

The images will be reviewed by Neuspera with the investigator prior to the implant procedure. Based on the analysis, if it is determined that the distance from the surface of the skin in the prone or seated position to the bone edge is greater than the capabilities of the system, then the subject will not be implanted with the Neuspera system.

For sacral thickness of 16.5 mm or less the SNS-28 neurostimulator is recommended for implant and for sacral thickness >16.5 mm, the SNS-35 is recommended for implant. Final device model implanted will be based on the investigator's assessment at the time of implant.

7.5.9.11 Cystoscopy

A cystoscopy will be required to assess and document exclusion criteria for the absence of bladder neck obstruction, presence or absence of urethral strictures, and other bladder pathology. A cystoscopy completed within 6 months of the screening baseline visit date is acceptable or a test conducted at screening baseline visit may be used to qualify the subject for trial entry.

7.5.9.12 Stimulation Characteristics/Programming Parameters

Data from the Wireless Transmitter and Clinician Programmer will be collected and saved during each visit.

7.5.9.13 Adverse Events

All adverse events (AEs) that occur to any subject during study participation must be documented on an AE case report form (CRF). Refer to section 8.4 for further reporting requirements.

7.5.9.14 Physician User Experience Questionnaire

The investigator will complete a Physician User Experience Questionnaire at the following time points:

- Phase I: At the time the first subject enrolled completes the final trial visit.
- Phase I: At the time the last subject enrolled completes the Month 3 visit.
- Phase II: At the time the last subject enrolled completes the Month 6 visit.

7.5.9.15 Subject User Experience Questionnaire

The subjects will complete a Subject User Experience Questionnaire at the following time points:

- Phase I: At the final trial visit (Day 21, 35 or 49) and at the Month 3 visit.
- Phase II: At the completion of the Day 28 or Day 42 visit and at the Month 6 visit.

7.5.9.16 Schedule of Assessments

Follow-up visits must occur according to the visit schedule. Follow-up visit windows will open when the prior visit is complete and will close when the sequential visit occurs. Below Table 6 and Table 7 provide details on Phase I follow-up schedule and required testing, Table 8 and Table 9 provide details on Phase II follow-up schedule and required testing.

TABLE 6 : PHASE I FOLLOW-UP SCHEDULE

	NOTE: OAB medication washout for at least five half-lives. Completed prior to baseline bladder diary
Visit	**Visit Target**
Screening/Baseline	N/A
Implant Visit	Within the six weeks following the Screening/Baseline Visit
SNS Trial Period 7-day Visit	7 (-/+2) days from Implant
SNS Trial Period 14-day Visit (telephone visit allowed if criteria met*)	14 (-/+2) days from Implant
SNS Trial Period 21-day Visit	21 (-/+2) days from Implant
SNS Trial Period 28-day Visit (if required) (telephone allowed visit if criteria met*)	28 (-/+2) days from Implant
SNS Trial Period 35-day Visit (if required)	35 (-/+2) days from Implant
SNS Trial Period 42-day Visit (if required) (telephone visit allowed if criteria met*)	42 (-/+2) days from Implant
SNS Trial Period 49-day Visit (if required)	49 (-/+2) days from Implant
Post-Trial Period Visit Schedule: Days (-/+) from Final Trial Visit	
Month 1 Clinic Visit: 30 (-/+ 14) days Month 1.5 Telephone Visit Month 2 Clinic Visit: 60 (-/+ 14) days Month 2.5 Telephone Visit Month 3 Clinic Visit: 90 (-/+ 14) days Month 3.5 Telephone Visit Month 4 Clinic Visit: 120 (-/+ 14) days Month 4.5 Telephone Visit Month 5 Clinic Visit: 150 (-/+ 14) days Month 5.5 Telephone Visit Month 6 Clinic Visit: 180 (-/+ 14) days Month 9 Clinic Visit 270 (-/+ 14) days Month 12 Clinic Visit: 360 (-/+14) days	Month 18 Clinic visit: 540 (-/+ 21) days Month 24 Clinic Visit: 720 (-/+ 21) days Month 30 Clinic visit: 900 (-/+ 21) days Month 36 Clinic Visit: 1080 (-/+ 21) days Month 42 Clinic Visit: 1260 (-/+ 21) days Month 48 Clinic Visit: 1440 (-/+ 21) days Month 54 Clinic Visit: 1620 (-/+ 21) days Month 60 Clinic Visit: 1800 (-/+ 21) days

TABLE 7 : VISIT PROCEDURE SCHEDULE – PHASE I

			SNS Trial Period			Post-Trial Period			Study Exit	
Procedure	**Screening/ Baseline**	**Baseline Assess-ments**	**Device Implant**	**SNS Trial Follow-up Period**	**Final Trial Visit**	**Clinic Visits Month 1 to 6 Every 3 Months to Month 12, every 6 Months to Month 60**	**Telephone Visits Monthly 1.5 to 5.5.**	**Unscheduled Follow-up Visit**	**Device Explant**	**30-Day Post-Explant F/U**
Informed Consent	X									
Inclusion/Exclusion	X		X							
Baseline Evaluation (Demographics, Medical History, OAB History, Physical Exam)	X									
Vital Signs	X		X	X		X			X	X
HbA1c	X									
Urinalysis	X									
Pregnancy Test (if applicable)	X									
Assessment of Subject's Sacral Anatomy	X									
Urodynamics (within 6 months)	X									
Cystoscopy (within 6 months)	X									
OAB Medication Washout (at least 5 half-lives)	X									
Medication Use and Changes (including OAB Medication) & Conservative OAB Therapies Log	X		X	X		X	X	X	X	X
Body Weight	X					Month 12, 24, 36, 42, 60				
Adverse Events	X		X	X		X	X	X	X	X
Wound Check				X	X					X
1-3 Day Post Implant Telephone				X						
Neurostimulator position confirmation image			X		X				X	
Therapy Review and Adjust Stimulation				X		X				
72-Hour Bladder Diary		X		X		X (Voided volume at Month 6 and 12)				
Stimulation Diary				X		X (Daily ≤ Month 12 Weekly > Month 12)	X			
Wexner Scale (only if FI)		X		X		X				
ICIQ-OABqol, ICIQ-MLUTS/FLUTS		X				X Month 3,6,12,24,36, 42, 48, 54, 60				
PGI-I						X Month 3,6,12,24,36, 42, 48, 54, 60				
Subject User Experience Questionnaire					X	X (Month 3)				
Device Explant									X	
Study Exit										X

TABLE 8 : PHASE II FOLLOW-UP SCHEDULE VISIT

Visits	**NOTE: OAB medication washout for at least five half-lives. Completed prior to baseline bladder diary**
Screening/Baseline Visit	
Implant Visit	Goal of within the six weeks following the date of Informed Consent but no later than 12 weeks after the 72-hour Baseline Bladder Diary
Post Implant Visit Schedule: Days (-/+) from Implant	
Day 7 Clinic Visit: 7 (-/+ 2) days Day 14 Clinic Visit: 14 (-/+ 2) days Day 21 Clinic Visit: 21 (-/+ 2) days Day 28 Clinic Visit: 28 (-/+ 2) days (Response Rate Assessment) Day 35 Clinic Visit: (if required): 35 (-/+ 2) days Day 42: Clinic Visit (if required): 42 (-/+ 2) days (Response Rate Assessment) responder at Day 28 Visit. Month 2 Clinic Visit: 60 (-/+ 14) days Month 3 Clinic Visit: 90 (-/+ 14) days Month 4 Clinic Visit: 120 (-/+ 14) days Month 5 Clinic Visit: 150 (-/+ 14) days Month 5.5 Telephone Visit Month 6 Clinic Visit: 180 (-/+14) days Month 9 Clinic Visit: 270 (-/+ 14) days Month 12 Clinic Visit: 360 (-/+ 14) days	Month 18 Clinic Visit: 540 (-/+ 21) days Month 24 Clinic Visit: 720 (-/+ 21) days Month 30 Clinic Visit: 900 (-/+ 21) days Month 36 Clinic Visit: 1080 (-/+ 21) days

TABLE 9 : VISIT PROCEDURE SCHEDULE – PHASE II

				Post-Implant				Study Exit	
Procedure	**Screening / Baseline**	**Baseline Assess-ment**	**Device Implant**	**Clinic Visit (Day 7, 14, 21, 28) & Day 35, 42 (if required)**	**Clinic Visits Month 2 to 6 Every 3 Months to Month 12, every 6 Months to Month 36**	**Telephone Visits At 5.5 months.**	**Unscheduled Follow-up Visit**	**Device Explant**	**30-Day Post-Explant F/U**
Informed Consent	X								
Inclusion/Exclusion	X		X						
Baseline Evaluation (Demographics, Medical History, OAB History, Physical Exam)	X								
Vital Signs	X		X	X	X			X	X
HbA1c	X								
Urinalysis	X								
Pregnancy Test (if applicable)	X								
Assessment of Subject's Sacral Anatomy	X								
Urodynamics (within 6 months)	X								
Cystoscopy (within 6 months)	X								
OAB Medication Washout (at least 5 half-lives of OAB medications)	X								
Medication Use & Changes (including OAB Medication) & Conservative OAB Therapies Log)	X		X	X	X	X	X	X	X
Body Weight	X				Month 12, 24, and 36				
Adverse Events	X		X	X	X	X	X	X	X
Wound Check				X					X
1-3 Day Post Implant Telephone Check				X					
Neurostimulator position confirmation image			X	X (Day 28 or Day 42)				X	
Response Rate Assessment				X (Day 28 and/or 42)					
Therapy Review and Adjust Stimulation				X	X				
72-Hour Bladder Diary		X (Voided volume required)		X	X (Voided volumes at Month 6 and 12)				
Stimulation Diary				X	X (Daily ≤ Month 12 Weekly > Month 12)	X			
Wexner Scale (if FI)		X		X	X				
ICIQ-OABqol, MLUTS/FLUTS		X			X (Month 3,6,12,24 & 36)				
PGI-I					X (Month 3,6,12,24 & 36)				
Subject User Experience Questionnaire				X (Day 28 or 42)	X (Month 6)				
Device Explant								X	
Study Exit									X

7.5.9.17 Equipment for Assessment

Prior to enrollment of a subject, the sponsor shall ensure that all products from the Neuspera Implantable SNS System are available for the investigator. If updates for the Patient Controller, Clinician Programmer, or Wireless Transmitter are available, the Sponsor shall ensure these updates are provided to the devices of the investigator and the investigator is instructed on how to update the Patient Controller and Wireless Transmitter on the next follow-up visit of each subject.

Equipment used for study assessments, outside of the Neuspera SNS System, are maintained according to the institute's standard operation procedures and hospital procedures.

7.5.9.18 Factors that may Compromise the Outcome of the Clinical Trial or the Interpretation of Results

Any known or foreseeable factors that may compromise the outcome of the clinical trial or the interpretation of results are, to the best of the Sponsor's knowledge, obviated by the inclusion and exclusion criteria, the clinical investigational plan, and careful definition of clinical investigation procedures and outcome analyses.

8 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

8.1 Definitions

8.1.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device. Definitions here are compatible with Regulation (EU) 2017/745 of the European Parliament.

This definition includes events that are anticipated as well as unanticipated events. This definition includes events occurring in the context of a clinical investigation related to the investigational device or the procedures involved. For the purpose of safety reporting all activities related to the use of a medical device may be considered procedures.

Any signs or symptoms associated with the reason for device replacement or explant should be reported as an adverse event (e.g. loss of stimulation).

Note: Because the protocol requires surgical procedures, mild pain, swelling, etc. should not be considered untoward and not considered an AE; however, any event that is more severe or lasts longer than typical should be considered an AE.

Subjects in the study, by definition, have UUI. Unless the UUI is worsened (more frequent or more severe), then UUI should not be considered untoward and should not be considered an AE.

Subjects may experience unpleasant sensations during the course of the device programming procedures. If the condition resolves immediately with re-programming, then these events should not be considered as untoward and are not AEs. Similarly, ongoing paresthesias should not be considered an AE unless they are bothersome to the subject.

8.1.2 Serious Adverse Event

A serious adverse event (SAE) is defined as an AE that led to any of the following:

a) Death,
b) Serious deterioration in the health of the subject, that resulted in any of the following;
    1) Life-threatening illness or injury, or
    2) Permanent impairment of a body structure or a body function, or
    3) Hospitalization or prolongation of 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,
    5) Chronic disease,
c) Fetal distress, fetal death or a congenital physical or mental impairment or birth defect.

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

In addition, per the FDA website:

https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event -

Other Serious (Important Medical Events) should be reported as a serious adverse event if the event does not fit the other outcomes cited above, but the event may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes cited above.

8.1.3 Device Deficiency

Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunctions, use errors, and inadequacy of information supplied by the manufacturer.

Malfunction

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical study protocol.

Use Error

Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

Inadequacy of Information Supplied by the Manufacturer.

Failure of an investigational medical device to perform in accordance with its instructions for use or visually not conform to the labeled device description.

8.1.4 Serious Public Health Threat

A serious public health threat means an event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time.

8.1.5 Adverse Device Effect

An adverse device effect is an adverse event related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

8.1.6 Serious Adverse Device Effect

A serious adverse device effect (SADE) is an adverse event that is both serious and device related.

8.1.7 Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan

or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

An event will not be considered a UADE if it is a known consequence of the underlying disease or condition under investigation, surgery, or other events that commonly occur in the study population independent of the investigational device.

The final determination of whether an AE meets the definition of a UADE will be made by the independent Clinical Events Committee for this study.

8.1.8 Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect (USADE) is any serious adverse device effect which by nature, incidence, severity or outcome has not been identified in the current risk assessment.

An event will not be considered a USADE if it is a known consequence of the underlying disease or condition under investigation, surgery, or other events that commonly occur in the study population independent of the investigational device.

The final determination of whether an AE meets the definition of a USADE will be made by the independent Clinical Events Committee for this study.

8.1.9 Anticipated Serious Adverse Device Effect

An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

8.2 Adverse Events Causality and Severity Rating

8.2.1 Causality

Safety reporting in clinical investigations of medical devices will be performed in line with the requirements of the Regulation (EU) 2017/745: Medical Device Regulation (MDR) Article 80(2), including the guidance document MDCG 2020-10/1. The relationship between the use of the investigational device (including the medical-surgical procedure) and the occurrence of each serious adverse event will be assessed and categorized using terms below. This guidance document only applies to serious adverse events; however, for ease of investigator reporting, Neuspera will use the same categorization terms for both serious adverse events and non-serious adverse events.

The investigator must specify whether an adverse event has a causal relationship to one of the following:

- **Study device:** Involves function of the device, or the presence of the device in the body, events directly related to the device.
- **Implant procedure:** Results from the implant procedure, including events directly related to the general procedural sequelae.
- **Subject's condition:** Results from the worsening of a pre-existing condition or cannot be attributed to the device procedure.
- **Unknown:** Cannot be assigned to any of the above three conditions.

The causal relationship of an adverse event to the investigational device or implant procedure will be rated as follows:

- **Not related:** Relationship to the device, comparator or procedure can be excluded when:
  - the event has no temporal relationship with the use of the investigational device or the procedures related to application of the investigational device;
  - the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
  - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
  - the event involves a body-site or an organ that cannot be affected by the device or procedure;
  - the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
  - the event does not depend on a false result given by the investigational device used for diagnosis[4], when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

- **Possible:** The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- **Probable:** The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot reasonably be explained by another cause.
- **Causal relationship:** the serious adverse event is associated with the investigational device, comparator, or with procedures beyond reasonable doubt when:
  - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
  - the event has a temporal relationship with investigational device use/application or procedures;
  - the event involves a body-site or organ that
    - the investigational device or procedures are applied to;

[4] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

    - the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis[5], when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

The adjudication decision of the CEC will be used for the final classification of events, including relatedness to the study procedures and/or the investigational device, for the determination of safety endpoints and for all regulatory reports, product labeling, and publications or presentations.

[5] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

8.2.2 Severity

All adverse events will have a severity classification according to the Clavien-Dindo classification system.[12,13]

Grades	Definitions
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Acceptable therapeutic regimens are: drugs such as antiemetics, antipyretics, analgesics, diuretics, and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic, or radiological intervention
Grade III-a	Intervention not under general anesthesia
Grade III-b	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications: brain hemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks) requiring IC (intermediate care)/ICU (intensive care unit) management
Grade IV-a	Single organ dysfunction (including dialysis)
Grade IV-b	Multi-organ dysfunction
Grade V	Death of a patient
Suffix “d”	If the patient suffers from a complication at the time of discharge the suffix “d” (for disability) is added to the respective grade of complication. This label indicates the need for a follow-up to evaluate the complication fully.

8.3 Foreseeable Adverse Events and Anticipated Adverse Device Effects

See Section 4.4 for risks associated with the Neuspera’s Implantable SNS System.

8.4 Reporting Requirements

8.4.1 Adverse Event Recording

Investigators are responsible for providing a description of all AEs, including the date of the event, treatment, and the clinical outcomes for the subject. Investigators will evaluate each event for seriousness, severity and relatedness to the procedure, device, or stimulation therapy. Investigators must supply the Sponsor with additional information related to safety reporting of a particular event.

Pre-existing conditions must be documented as medical history so that related AEs can be correctly recorded. An event that is a continuation of an unresolved AE must be recorded as ongoing, not as a new AE. Worsening of a pre-existing condition must be recorded. Complications and hospitalizations must also be recorded.

Sponsor shall fully record any adverse event of a type identified in the clinical investigation plan as being critical to the evaluation of the results of the clinical investigation.

8.4.2 Adverse Event Reporting

Investigators are required to report all AEs during the course of the study (except as outlined below).

Investigators shall report AEs to the Sponsor, and to their reviewing IRB/ECs per the IRB/EC reporting requirements.

Investigators are required to report UADEs to the Sponsor and their reviewing IRB as soon as possible but in no event later than 10 working days after the Investigator first learns of the effect, per 21 CFR 812.150. Per MDCG 2020-10/1, UADE shall immediately be reported by the investigators, but no later than 3 calendar days after investigational site study personnel's awareness of the event.

AE reporting exceptions:

- AEs that would be reasonably expected to be associated with any surgical procedure (e.g. anesthesia associated symptoms, surgical site pain, post- procedure pain) will not be required to be reported as AEs unless, in the opinion of the Investigator, the nature and/or severity is outside of what is typical for SNS procedures and recovery.

8.4.3 Emergency Contact Details for Reporting Serious Adverse Events and Serious Adverse Device Effects

In the event of an emergency the following individual may be contacted at the sponsor organization:

Mark Vollmer

Clinical Director, Neuspera Medical

Mark.vollmer@neuspera.com

1-612-281-4875

8.4.4 Reporting Device Deficiencies

Investigators are responsible for providing a description of all device deficiencies, including any impact on the subject. Notification of device deficiencies should be made to the Sponsor or representative as soon as possible for appropriate investigation. Device deficiencies are reported on the appropriate case report form.

The investigator shall report initially (and any new findings) and the sponsor shall fully record and report without delay to all EU Member states in which the study is occurring any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate. Sponsor shall report this without delay per applicable guidelines and local regulations.

The period for reporting shall take account of the severity of the event. Where necessary to ensure timely reporting, the sponsor may submit an initial report that is incomplete followed up by a complete report.

8.4.4.1 Events or Malfunctions (Lead Migration/Dislodgement, Fractures, Revisions)

Investigators shall report to Neuspera as soon as possible but no event later than 30 working days after the investigator first learns of the effect of all device events or malfunctions, that is, lead migration/dislodgement and fractures, whether clinically significant or not. In addition, a further breakdown of how device events or malfunctions are dealt with will be provided (e.g. no action needed, reprogramming, permanent loss of therapy and/or surgical revision/explantation). These events will be recorded by subject and event, since multiple events may occur in a single subject.

All events (lead migration/dislodgement and fractures), whether determined to be clinically significant or non-clinically significant, will be identified and reported to the DSMB and the FDA as soon as possible but in no event later than 10 working days after Neuspera first receives notice of the event from the clinical investigator.

Clinically significant events are those events that can only be corrected by surgical revision or result in permanent loss of therapy. If the therapy is still providing benefit after reprogramming, Neuspera considers the event not to be clinically significant. Any investigator who corrects a clinically significant event of lead migration/dislodgement, fracture, and loss of therapy with a revision surgery will be asked to notify Neuspera as soon as possible but in no event later than 30 working days after the investigator completes the revision surgery. Neuspera anticipates that Field Clinical Engineers will support all revision surgeries, and Neuspera will then report any clinically significant events of lead migration/dislodgement, fracture, and loss of therapy corrected by revision surgery to the FDA and DSMB as soon as possible but in no event later than 10 working days.

8.4.5 Reporting Serious Adverse Events and Serious Adverse Device Effects

Investigators shall report SAEs and SADEs to the Sponsor, and to their reviewing IRB/ECs per the IRB/EC reporting requirements. Investigators are required to report SADEs to the Sponsor and their reviewing IRB as soon as possible but in no event later than 10 working days after the Investigator first learns of the effect, per 21 CFR 812.150. Per MDCG 2020-10/1, SAE and SADEs shall immediately be reported by the investigators, but no later than 2 calendar days after investigational site study personnel's awareness of the event for reportable events which indicate an imminent risk of death, serious injury, or serious illness and that require prompt remedial action for other subjects, users or other persons or a new finding.

Sponsor shall report any SAE that has a causal relationship with the investigational device or the procedure or where such causal relationship is possible, without any delay per applicable guidelines and local regulations. This is also applicable for any new findings in this category. Per MDCG 2020-10/1 these SAEs should be reported immediately, but not later than 7 calendar days following the date of awareness.

8.5 Sponsor Responsibilities

The Sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation and shall:

A. Review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the Sponsor and the

principal investigator(s), the sponsor shall communicate both opinions to concerned parties, as defined in b and c given below

B. Report or ensure the reporting, to the Ethics Committees by the principal investigators(s), of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the Ethics Committee.
C. Report to regulatory authorities, within the required time period, all serious adverse events and device deficiencies that could have led to a serious adverse device effect, including serious health threat
D. Inform all principal investigators in writing of all the serious adverse events at all investigation sites that have been reported to the Sponsor, and ensure that they are reported to their Ethics Committee, if required by the Ethics Committee: this information shall be sent to all the principal investigators within a time frame established based on the perceived risk as defined in the risk assessment (analysis and evaluation)
E. Ensure that the Ethics Committees and the regulatory authorities are informed of significant new information about the clinical evaluation
F. In case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

8.6 Investigator Responsibilities

The principal investigator shall:

A. Record every adverse event and observed device deficiency, together with an assessment
B. Report to the Sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports
C. Report to the Ethics Committees serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the Ethics Committee
D. Report to regulatory authorities serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the Ethics Committee

Supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.

9 SITE INITIATION ACTIVITIES

9.1 Investigator and Site Selection

The Sponsor will assess potential investigators to ensure that they are experienced and have the necessary expertise. Investigators must have the ability to enroll an adequate number of subjects.

The Sponsor will assess the site to ensure that it is equipped with adequate facilities for the study. The Sponsor will ensure that qualified personnel are available to conduct the study, including a designated research coordinator.

Investigators must agree to comply with this protocol, all institutional review board requirements/ethics committee requirements, and all applicable laws and regulations.

9.2 Initiation Requirements

Investigative sites may begin enrolling subjects after all initiation requirements are met and the Sponsor has given notice of approval to start. Initiation requirements include Institutional Review Board (IRB)/Ethics Committee (EC) approval of this protocol and the informed consent, training of all participating site personnel, a site initiation visit by the Sponsor, and submission of all required documents to the Sponsor. Required documentation includes IRB/EC approvals, curricula vitae (CVs), signed investigator agreements, conflict of interest/financial disclosure statements, documentation of site training, and any other documents requested by the Sponsor.

9.3 Site Training

The Investigator Brochure (IB) will be provided to the principal investigator who shall acknowledge the receipt in writing. On-site training of investigators and site study personnel will be conducted by the Sponsor as part of the initiation activities. Training sessions may be tailored to fit site personnel's roles in the study. The Sponsor will ensure adequate training is provided on the following:

- Investigational device, principle of operation and system components
- Device implant and explant procedures
- Neuspera's SNS System Instructions for Use
- Protocol
- Data collection and CRFs
- Diary instructions for use
- Investigator responsibilities
- Device accountability
- Good Clinical Practice

10 ETHICS

10.1 Ethics Review

The final study protocol and written Informed Consent must be approved in writing by an IRB or EC, as applicable. The principal investigator is responsible for informing the IRB/EC of any amendments to the protocol in accordance with local requirements. In addition, the IRB/EC must approve all advertising used to recruit subjects to the study. The protocol must be re-approved by the IRB/EC annually, as local regulations require.

Progress reports and notifications of serious, unexpected adverse events will be provided to the IRB/EC according to local regulations and guidelines.

10.2 Ethics Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regional regulatory requirements.

10.3 Written Informed Consent

Written Informed Consent must be obtained prior to any study-related procedure. Electronic or written informed consent will be obtained in compliance with local regulations. The Principal Investigator will ensure that proper informed consent is conducted, including ensuring the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects will have appropriate time to review the Informed Consent, ask questions and will be provided with additional information as requested. When new information becomes available during the study, subjects will be informed as needed. Subjects must also be notified that they are free to discontinue/withdraw from the study at any time. The subject must be given the opportunity to ask questions and allowed time to consider the information provided.

A copy of the consent document must be provided to the subject and the original signed consent document should be retained in the study records. Any modifications made to the informed consent form must be approved by the IRB/EC and Sponsor.

10.4 Subject Withdrawal

A subject's participation in the study is voluntary. Subjects may withdraw their consent from participation in the study at any time. Should a subject exit the study for any reason, the investigator will document the reason for study exit, if known and record in the study database.

11 DATA MANAGEMENT

11.1 Contract Support Groups

Three external organizations have been retained to manage aspects of the SANS-UUI study.

Fortrea, Inc. – Medical Device & Diagnostic Development
8 Moore Drive
Durham, North Carolina 27703, USA

The Sponsor has identified an independent statistician at Fortrea a third-party to conduct the interim analysis.

Axiom Real-Time Metrics
5205 Satellite Dr.
Mississauga, Ontario, Canada
L4W 5P9

Axiom, refer to as "the CRO" is responsible for overall study management including monitoring, study reports, Trial Master File, safety, and data management including management of the CEC and DSMB. Axiom will be providing and managing the EDC including all subject reported outcomes.

AVANIA Europe -Bilthoven
3723 MB Bilthoven
The Netherlands
+31 30 299 2727

AVANIA is responsible for providing requirements to achieve ethics committee (EC) and competent authority (CA) approvals for the clinical trial in Canada and Europe. Avania reviews submissions prior to submitting to the EC and CA as well as manages all correspondence with the EC and CA on behalf of Neuspera as Neuspera's local representative in Europe.

The sponsor may retain additional contractors and/or replace the contractors listed above; a current list of the retained contractors will be maintained in the Manual of Operations.

11.2 Subject Identification

Each subject will be assigned a unique identification code (ID) for the purpose of identity protection. Any subject names that may inadvertently appear on study documents submitted to the Sponsor will be redacted upon receipt.

11.3 Central Database

All study documentation, not including subject data, will be collected, and stored using an electronic Trial Master File. The CRO will use appropriate quality control measures established to ensure accurate and complete transfer of information from the study documentation to the central database following internal Standard Operating Procedures.

11.4 Case Report Forms

An electronic data capture system will be used to collect subject data on case report forms. The investigator is responsible for completing all appropriate sections of the CRFs and submitting them to the Sponsor in a timely manner. The investigator is also responsible for responding to queries from the Sponsor to clarify any pending questions about the data.

11.5 Protocol Deviations

An Investigator is required to conduct this study in accordance with the signed Clinical Trial Agreement and Investigator Agreement, study protocol, regulatory requirements, Good Clinical Practice, Declaration of Helsinki, and any conditions of approval imposed by the reviewing IRB/EC and FDA.

In accordance with applicable regulations, under emergency circumstances, deviations from the Clinical Investigational Plan to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the Investigational Review Board / Ethics Committee. Such deviations shall be documented and reported to the sponsor and the Investigational Review Board / Ethics Committee as soon as possible, but no later than five (5) working days after the emergency occurred.

The investigator must document any deviation to this protocol using the appropriate CRF. Except in an emergency, prior approval by the Sponsor is required for an anticipated change in or deviation from the plan and if these changes or deviations could affect the scientific soundness of the plan or the rights, safety or welfare of human subjects, prior FDA and IRB/EC approval is also required.

No waivers for deviations from the clinical investigation plan will be provided by the study sponsor. Waivers are strictly prohibited.

11.6 Corrective and Preventive Actions

Neuspera or its representatives will evaluate deviations to the clinical investigation plan during monitoring visits. Individual event corrective and preventive actions may be recommended at that time. In addition, deviations occurring across investigational sites will be reviewed by Neuspera on a periodic basis to determine if more global preventive actions may be required.

11.7 Investigator Disqualification Criteria

Neuspera reserves the right to terminate an investigator/investigational site for any of the following reasons:

- Failure to secure subject informed consent including protection of personal data prior to enrollment
- Failure to report safety events within 10 working days of discovery after learning of the event
- Failure to report serious adverse device effects within 10 working days of discovery
- Repeated investigational plan deviations
- Repeated failure to appropriately complete case report forms
- Failure to enroll an adequate number of subjects
- Loss of or unaccounted for investigational product inventory

11.8 Site Noncompliance

Protocol deviations will be closely monitored. If unacceptable deviations, repeated deviations, or other compliance problems are noted, the Sponsor reserves the right to suspend study enrollment or discontinue study enrollment at that site until a sufficient system is in place to reduce further deviations and ensure compliance.

11.9 Data Processing and Management

Data will be reviewed manually and electronically for accuracy and completeness. Standard checks such as range checks will be incorporated into the central database. Queries will be issued to resolve data discrepancies. Study monitoring will be conducted to ensure that the site is submitting complete and accurate data, and to verify source data. The CRO will use appropriate quality control measures established to finalize and lock the database following internal Standard Operating Procedures.

The CRO maintains Standard Operating Procedures for CRF tracking, data review, database cleaning, and issuing and resolving queries. The CRO maintains timely and reliable processes for recording data and rectifying errors and omissions, medical coding uniformity and reconciliation to ensure delivery of a quality database to support the implementation of the planned analyses. These systems maintained by the CRO are also supported by the study Data Management Plan and the Clinical Management Plan.

11.10 Data Protection

11.10.1 Subjects Enrolled in the US

In accordance with the Health Portability and Accountability Act (HIPAA), the written Informed Consent Form must include a subject authorization to release medical information to the study Sponsor and/or allow the Sponsor or their designate, a regulatory authority, or IRB/EC access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

11.10.2 Subjects Enrolled in Canada

In accordance with the Personal Information Protection and Electronic Document Act (PIPEDA). The written Informed Consent Form must include collection, use and disclosure of personal information. Subjects must be provided clear information explaining what organizations are doing with their information. Therefore, the written Informed Consent Form must include a subject authorization to release medical information to the study Sponsor and/or allow the Sponsor or their designate, a regulatory authority, or IRB/EC access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

11.10.3 Subjects Enrolled in Europe

Data protection will be ensured in accordance with Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR). Personal data shall be:

- processed lawfully, fairly and in a transparent manner in relation to the data subject ('lawfulness, fairness and transparency');
- collected for specified, explicit and legitimate purposes and not further processed in a manner that is incompatible with those purposes; further processing for archiving purposes in the public

interest, scientific or historical research purposes or statistical purposes shall, in accordance with Article 89(1), not be considered to be incompatible with the initial purposes ('purpose limitation');

- adequate, relevant and limited to what is necessary in relation to the purposes for which they are processed ('data minimization');
- accurate and, where necessary, kept up to date; every reasonable step must be taken to ensure that personal data that are inaccurate, having regard to the purposes for which they are processed, are erased or rectified without delay ('accuracy');
- kept in a form which permits identification of data subjects for no longer than is necessary for the purposes for which the personal data are processed; personal data may be stored for longer periods insofar as the personal data will be processed solely for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes in accordance with Article 89(1) subject to implementation of the appropriate technical and organizational measures required by this Regulation in order to safeguard the rights and freedoms of the data subject ('storage limitation');
- processed in a manner that ensures appropriate security of the personal data, including protection against unauthorized or unlawful processing and against accidental loss, destruction, or damage, using appropriate technical or organizational measures ('integrity and confidentiality').

11.11 Confidentiality and Protection of Study Files

All information and data concerning subjects and their participation in this study will be considered confidential. Only authorized personnel will have access to confidential files. Passwords will be issued for Sponsor personnel to ensure confidentiality and protection of electronic data. Hard copy data will be stored in a locked file. No data will show subject names.

11.12 Monitoring

The Sponsor will be responsible for monitoring at each site to ensure adequate protection of the rights and safety of study subject, and to verify the quality and integrity of the data collected and submitted. The Sponsor will identify and train qualified personnel to conduct monitoring visits. Monitoring will consist of review of subject records, source documents, and other required documentation, including IRB/EC approvals and correspondence.

Monitors will conduct site visits to ensure accuracy of data, timeliness of data submission, adequate subject enrollment, compliance with applicable laws and regulations, compliance with this protocol, compliance with the signed investigator agreement, and compliance with IRB/EC conditions and guidelines. Any noncompliance with these items that is not adequately addressed by the investigator is cause for the Sponsor to put the investigator on probation or withdraw the investigator or site from the study.

The site staff must be available to meet with the monitor or other Sponsor representative during monitoring visits. The investigator must allow monitoring by the Sponsor and its authorized

representatives and any other local governmental body to review the study subjects' medical records, including any test or laboratory data.

Frequency of monitoring will be based on enrollment, study duration, site compliance, and any suspected inconsistency in data that requires investigation. During the COVID-19 pandemic monitoring visits may be conducted remotely.

11.13 Audits and Inspections

Audits of the study sites may be performed by the Sponsor or designee, independent of and separate from routine monitoring or quality control functions, to evaluate study conduct and compliance with the study protocol, applicable regulatory requirements, GCP, Declaration of Helsinki, and any conditions of approval imposed by the reviewing IRB and FDA.

The FDA or other regulatory agencies may perform inspections of the study sites before, during or after the conclusion of the study. The investigator shall contact the Sponsor immediately upon notification of inspection and must fully cooperate with the regulatory agency by permitting inspections at reasonable times and in a reasonable manner.

11.14 Access to Study Records

The Investigator must permit monitoring and auditing by the Sponsor or designee, and inspection by the appropriate regulatory authorities, and provide direct access to all requested study-related records.

11.15 Record Retention

The investigator and Sponsor shall maintain the required records during the investigation and for a period of 2 years, or country specific reporting requirement if different than 2 years, after the latter of either the completion/termination of the study or the date the Neuspera Implantable SNS System receives market approval for the indication being studied.

The clinical investigation will be conducted in Canada. Canada Food and Drug Regulation requires the sponsor to maintain all trial related records for a period of 15 years.

As the investigation will be conducted at centers in Europe, consistent with the new European medical device requirements, documentation shall be kept for a period of at least 15 years after the clinical investigation with the device has ended or in the event that the device is subsequently placed on the market, at least 15 years after the last device has been placed on the market.

An investigator or Sponsor may withdraw from the responsibility to maintain records for the period required and transfer custody of the records to any other person who will accept responsibility for them.

The investigator's study records may be discarded only upon approval from the Sponsor. The investigator must contact the Sponsor before destroying any records pertaining to the study to ensure that they no longer needed to be retained.

12 RESPONSIBILITIES

This study will be performed in conformance with this protocol and all applicable laws and regulations.

12.1 Investigator Responsibilities

12.1.1 Coordinating Investigator

The sponsor will assign one investigator in the trial as the Coordinating Investigator. This investigator is assigned the responsibility for the coordination of investigators at the different centers participating in the trial. These responsibilities may include but are not limited to:

- Meeting regularly with the sponsor to review progress in the trial
- Review clinical management issues which may involve correspondence with one of the clinical investigators
- Review inclusion / exclusion criteria for potential trial participants as needed
- Review and provide consultation on individual adverse events
- Review and provide consultation on the clinical protocol, case report forms, informed consent, investigator's brochure
- Review and provide consultation on clinical and regulatory submissions

12.1.2 Investigator Responsibilities for Centers Participating in the Clinical Trial

The Investigator is responsible for ensuring the study is conducted according to the signed Clinical Trial Agreement (CTA)/Investigator Agreement (IA), study protocol, regulatory requirements, GCP, Declaration of Helsinki, and any conditions of approval imposed by the reviewing IRB and FDA; for protecting the rights, safety, and welfare of subjects under the Investigator's care; and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with the regulations.

12.1.3 Specific Responsibilities of Investigators

Awaiting approval. An investigator may determine whether potential subjects would be interested in participating in an investigation, but shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB and FDA approval.

Compliance. An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, 21 CFR part 812 and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

Supervising device use. An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under 21 CRF part 812 to receive it.

Disposing of device. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

12.1.4 Investigator Agreement and Financial Disclosure

The Principal Investigator at each site will be required to sign the Investigator's Agreement, as per applicable regulations.

In addition, in accordance with regulations, all investigators will be required to sign a Financial Disclosure form, which discloses the Investigator's and his/her immediate family's financial interests and arrangements with Neuspera. Investigators must inform the Sponsor of any changes to the information within the financial disclosure throughout the course of the study and for a period of two years after the device is approved by the FDA or the study is terminated, whichever is later.

12.1.5 Investigator Records

Participating investigators will maintain in the study site's essential study files accurate, complete and current records relating to the investigator's participation:

- Study protocol and all amendments
    - with documents showing the dates of and reasons for each deviation from the protocol.
- Signed Investigator Agreement for the Principal Investigator
- Signed Financial Disclosure for all investigators
- IRB/EC approval letters(s) including approved consent and HIPAA authorization form(s), and subject materials
- IRB membership list(s) or Letter of Assurance
- All correspondence with another investigator, an IRB or EC, sponsor, a monitor, FDA or regulatory authority, including required reports.
- Curriculum Vitae (CV) for all investigators
- Training documentation
- Delegation of Authority
- Investigational device accountability records including date of receipt, quantity, lot/serial numbers of all devices, device use and final disposition of the device.
- Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of
- Names of all persons who received, used, or disposed of each device.

The following records must be maintained for each subject enrolled in the study:

- Signed informed consent form and Authorization for the Use and Disclosure of Health Information. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
- For any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent.
- Case report forms and supporting documentation
- AEs and any supporting documentation
- Medical history, physical exams and results of diagnostic tests
- Information regarding exposure to the device

- Protocol deviations
- Source documentation: complete medical records, including procedure reports, professional notes, radiographic images, etc.

12.1.6 Investigator Reports

Investigators are required to prepare and submit the following complete, accurate, and timely reports:

- An investigator shall submit to the Sponsor and to the reviewing IRB/EC a report of any UADE/USADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
- The investigator shall report initially (and any new findings) to the sponsor any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
- An investigator shall report to the Sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB/EC of the investigator's part of an investigation.
- An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
- An investigator shall notify the Sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the Sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, prior FDA and IRB/EC approval in accordance with applicable regulations also is required.
- If an investigator uses a device without obtaining prior informed consent, the investigator shall report such use to the Sponsor and reviewing IRB/EC within five (5) working days after the use occurs.
- An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the Sponsor and the reviewing IRB.
- An investigator shall, upon request by a reviewing IRB/EC or FDA, provide accurate, complete and current information about any aspect of the investigation.

12.1.7 Investigator Contact Information

The CRO maintains a Neuspera Study Contacts list that contains information on each investigational site including the coordinating investigator, the address details for each investigational site and the contact information for the principal investigator at each site. This information will be stored in the electronic trial master file Clinical Trial Management System. This information is accessible for reporting serious adverse events and serious adverse device effects.

12.2 Sponsor Responsibilities

Neuspera Medical Inc. is the Sponsor of this study and is responsible for selecting qualified investigators and providing them with the information they need to conduct the study properly, ensuring proper monitoring of the study, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about the study. Sponsor responsibilities include, but are not limited to, the following:

- Select and qualify investigative sites and principal investigators
- Provide training to investigators and investigative site staff
- Ensure approval/permission from FDA
- Select qualified monitors and ensure that adequate monitoring of clinical data occurs at the study sites
- Retain ownership of all data generated in this study, and control the use of the data for appropriate purposes only
- Collaborate with investigators on publishing study results

12.2.1 Sponsor Representatives

Sponsor representatives may participate in the conduct of the study to the extent described in this protocol. Participation in the study will be limited to Sponsor personnel who are appropriately trained. Sponsor representative's tasks may include:

- Provide training to the investigator and study staff.
- Clarifying device behavior, operation, and output
- Provide technical support and direction during the Neuspera Implantable SNS System implant and explant procedures including operating the external stimulator for the Neuspera system during intraoperative testing under the direction of the investigator, and address procedure and device questions.
- Device Parameter/Download – download information from the Wireless Transmitter to the Neuspera device database
- Be available (in person or on the phone) during subject follow-up visits to provide technical support on programming and use of the Neuspera SNS system.

At no point shall personnel from the Sponsor:

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the oversight of a healthcare professional

12.3 Physician Review Panel

A Physician Review Panel experienced in the implant of sacral neuromodulation devices will be established. The panel will consist of at least two physicians. The physicians may or may not be investigators in the trial. The physicians will review all required study eligibility data prior to making a recommendation on subjects for implant in the trial. Reviews will be divided among the physicians. Investigators in the trial may not review subjects from their own center. The Physician Review Panel operations will be formalized in a charter.

12.4 Clinical Events Committee (CEC)

An independent Clinical Events Committee (CEC) will be established. The CEC will consist of clinicians who are not investigators in the study and who do not have any significant investment in the Sponsor or its competition. At least three clinicians will serve on the CEC.

The CEC will be responsible for reviewing and classifying all adverse events, including deaths. Adverse events will be reviewed for causality and seriousness.

The CEC will meet periodically throughout the study. CEC operations will be formalized in a CEC charter.

The CEC will review all adverse events and adjudicate causality and seriousness. The definitions to be used during the adverse event review and classification process are outlined in the study protocol. If the CEC adjudication is different than what was documented by the investigator there will be a notification to the investigator. The adjudication of the CEC will be used for the final classification of events.

The adjudication decision of the CEC will be used for the final classification of events, including relatedness to the study procedures and/or the investigational device, for the determination of safety endpoints and for all regulatory reports, product labeling, and publications or presentations.

The CEC will also be responsible for reviewing post implant neurostimulator images, following the image review by the implanting physician, to determine if movement has occurred. If the CEC assesses that movement has occurred, that has not been documented by the implanting physician, there will be follow-up discussion with the implanting physician and CEC facilitated by the sponsor or CRO. If final disagreement between the CEC members, or if there is disagreement between the implanting physician and the CEC, the DSMB will be notified for final assessment.

12.5 Data Safety Monitoring Board (DSMB)

An independent DSMB has been established. Members are not investigators in the study and all members do not have any significant investment in the Sponsor or its competition.

The DSMB has reviewed all safety data, has provided recommendations on the daily stimulation duration that are consistent with the Phase II trial design, and supports the trial expansion to the pivotal Phase II.

The DSMB will continue to monitor safety data in Phase I of the trial and also Phase II. The DSMB will meet following the implant of approximately every 36 subjects during Phase II of the study until completion of the 120 attempted implants. The DSMB may meet more frequently if determined necessary by the Sponsor, CRO or FDA based on adverse event rates, stopping rules and perceived risk of the study device and procedures in Phase I and II. Phase II study stopping rules based on event rates for

fractures, dislodgements/migrations and surgical revisions will be monitored by the DSMB following guidance presented in Study Stopping Rules for Phase II (Section 6.4). The DSMB report and meeting minutes will be provided to the FDA after each DSMB meeting. Enrollment in Phase II of the trial will continue unless one of the study stopping rules is met or the DSMB or FDA makes a recommendation to stop the enrollment and implantation of new subjects in the clinical trial.

DSMB will make the final review assessment of radiological images assessed by the CEC for movement if there is a disagreement between CEC members, or if there is disagreement between the implanting physician and the CEC.

DSMB operations are formalized in a DSMB charter.

12.6 Publications Committee

The Sponsor may form a publications committee to make decisions regarding authorship and content of publications. Neuspera's criteria for authorship may include involvement in the design and development of the clinical trial, enrollment of subjects, quality of data, experience with authorship and presentation at major journals and congresses, respectively. Publication of clinical data will conform to standards set forth in peer-reviewed journals and Uniform Requirements for Manuscripts Submitted to Biomedical Journal published by the International Committee of Medical Journal Editors (ICMJE). All publications must be reviewed and approved in advance by the Sponsor. Publication timing will occur as early as within one year of study completion. Publication during the duration of the trial is forbidden without review and agreement by the publication committee.

13 STUDY MATERIAL AND PRODUCT

13.1 Shipping

An initial supply of the investigational products will be shipped to the investigational site when the site is approved by the Sponsor after all requirements, such as IRB/EC approval, are completed. Resupply of investigational products during the study will be facilitated by the Sponsor, and/or designate.

13.2 Labeling

Labeling of the investigational devices will be performed in accordance with Good Manufacturing Practices (GMP) for Medical Devices of the Quality System Regulations (QSR). The devices will be labeled with the statement "CAUTION: Investigational device. Limited by Federal (or United States) to investigational use. Exclusively for Clinical Investigations."

Information on the investigational device label will indicate the identity, quantity, and storage conditions.

13.3 Storage

All investigational devices must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions will be specified on the device label and/or the appropriate Instructions for Use (IFU). The stored device supplies must be accessible to authorized staff only. The storage area must also have adequate control of temperature in order to maintain stability of the device supplies, according to the appropriate IFU. The investigational devices should be stored in the original pack until use. For further information, investigators should refer to the investigational device label and/or appropriate IFU.

13.4 Product Accountability

Sponsor description of procedures for accountability of investigational devices is outlined in the Neuspera Study Device Management Plan and SOP on Investigational Device Accountability. Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the Clinical Investigational Plan. The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal. The sponsor shall have instructions in place and make packaging materials available, if applicable, for the safe return or disposal of investigational devices, including potentially hazardous devices. The principal investigator or an authorized designee shall keep records documenting the following:

a) name(s) of person(s) who received, used, returned, or disposed of the device;
b) the date of receipt, identification, and quantity of each investigational device (i.e., batch number/serial number or unique code);
c) the expiry date, if applicable;
d) the date or dates of use;
e) subject identification;
f) date on which the investigational device was returned/explanted from subject, if applicable;

g) the date of return of unused, expired, or malfunctioning investigational devices, if applicable;
h) the date and documentation of disposal of the investigational devices as per instructions of the sponsor, if applicable.

All explanted devices must be returned to the Sponsor. Subjects may dispose of used custom undergarments or Wearable at their discretion. At study closeout, the Sponsor will collect all unused devices.

14 STUDY AMENDMENTS AND CLOSURE

14.1 Amendments to the Protocol

Any amendments to the study protocol will be clearly documented and approved by the Sponsor and the IRB/EC prior to implementation. Appropriate training will be completed on the study protocol amendment.

14.2 Suspension or Early Termination

The Sponsor reserves the right to suspend or terminate the study at an individual study site or entirely at any time. Suspension or early termination of a study site may occur due to serious or repeated non-compliance on the part of an investigator. There are no criteria for termination of the clinical investigation on statistical grounds.

Reasons for suspension or early termination of the entire study may include, but are not limited to, the following:

The incidence and seriousness of AEs in this or other studies indicates a potential health hazard to subjects;
New information on efficacy from this or other studies
In the event of suspension or early termination, the Sponsor will promptly inform principal investigators and ensure that IRB/ECs are notified of the stoppage and the reason for it. Subjects must continue to be followed per the protocol unless there is other direction from the Sponsor. If the trial is terminated, the sponsor will notify the FDA and all reviewing IRBs within 30 days. The sponsor will submit a final report to the FDA and all reviewing IRBs and participating investigators within 6-months after termination of the investigation.

Suspension or (Early) Termination language in the Clinical Trial Agreement for clinical sites in Canada and the EU will supersede the wording listed in this section.

14.3 Routine Closeout

At the end of the study, routine closeout activities will be conducted to ensure site records are complete, study data are complete and accurate, remaining study materials and investigational devices are returned to the Sponsor, arrangements are made for record retention, and IRB/ECs are notified.

14.4 Final Study Report

At the completion of the trial, the sponsor will notify the FDA and all reviewing IRBs within 30 days. The sponsor will submit a final report to the FDA and all reviewing IRBs and participating investigators within 6-months after completion of the investigation.

15 CLINICAL TRIALS REGISTRY (CLINICALTRIALS.GOV)

This study will be registered on www.clinicaltrials.gov and the results will be made public through the website. Study Results will be submitted as required. Per the regulatory requirements, the informed consent form will contain a statement that the clinical trial information will be entered into this registry.

16 STATEMENTS OF COMPLIANCE

This clinical investigation will be conducted in compliance with the principles that have their origin in the latest version of the Declaration of Helsinki, this clinical investigation plan, requirements of the approving Ethics Committees, ISO 14155, MDD 93/42/EEC Annex X – Clinical Evaluation, AIMDD 90/385/EEC, Regulation (EU) 2017/745 of the European Parliament and of the Council Article 120.11 (EU Medical Device Regulation), United States Food and Drug Administration Code of Federal Regulations Title 21 Parts 11, 50, 54, 56, 58 and 812 and other applicable regulatory requirements whichever provides the greater protection of the individual.

This clinical investigation will not be initiated until approval has been obtained from the applicable Ethics Committees. Any requirements imposed by the applicable Ethics Committees will be followed. No deviation from the clinical investigation will be implemented without the prior review and approval of the applicable Ethics Committees except where it may be necessary to eliminate an immediate hazard to a subject. In such case, the deviation will be reported to the applicable Ethics Committees in accordance with their specific reporting policies and procedures.

A human subject insurance will be secured prior to the start of the clinical investigation.

17 VULNERABLE POPULATION

The subject population of this clinical investigation does not meet the criteria for a vulnerable population as defined in ISO 14155, Section 3.55 and ICH-GCP, Section 1.61. If a subject loses ability to consent during the course of the clinical investigation, this will lead to study exit. Such subjects will be followed for safety for the course of the study, but their data will not be used for data analysis.

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19 APPENDIX A: PHASE I SUB-STUDY

Addendum to the SANS-UUI Study Protocol: Phase I Sub-Study to Assess The Benefit of Half-Hour Daily Stimulation

Short Title: SANS-UUI Phase I Sub-Study
Protocol Number: NSM-004
Version: 1.0
Version Date: 04 April 2025

Neuspera Medical Inc.
51 Daggett Drive
San Jose, CA 95134, USA
Telephone: +1 408.612.7570

SPONSOR SIGNATURE PAGE

The present study has been reviewed and approved.

Mark Vollmer	Director of Clinical Research
Sponsor representative (print)	Title
DocuSigned by: Mark Vollmer 9E2047ACEEB4E3...	2025-Apr-04
Signature	Date

INVESTIGATOR SIGNATURE PAGE

Title: Addendum to the SANS-UUI Study Protocol: Phase I Sub-Study to Assess Benefit of Half-Hour Daily Stimulation

Protocol ID: NSM-004

Investigator's statement

I agree to conduct this study in accordance with the design and specific provisions of this protocol; modifications to the study are acceptable only with a mutually agreed upon protocol amendment as approved by the Sponsor and the Institutional Review Board or the Ethics Committee. I agree to await Institutional Review Board or Ethics Committee approval of the protocol and informed consent before initiating the study, to obtain consent from subjects prior to their enrollment in the study, to collect and record data as required by the protocol and case report forms, and to maintain study documents for the period of time required.

Confidential

This document contains confidential information belonging to Neuspera Medical Inc. except as may be otherwise agreed to in writing, by accepting or reviewing these materials, I agree to hold such information in confidence and not to disclose it to others (except where required by applicable law), nor use it for unauthorized purposes.

_____

Investigator name (print)

_____

Signature Date

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REVISION HISTORY

Version	Date	Summary of Changes/ Affected Sections
01	04 April 2025	Initial release

SYNOPSIS

Clinical investigation plan	
Sub-study Title	Addendum to the SANS-UUI Study Protocol: Phase I Sub-Study to Assess Benefit of Half-Hour Daily Stimulation
Main Study Title	Clinical Study of Neuspera's Implantable Sacral Nerve Stimulation (SNS) System in Patients with Symptoms of Urinary Urgency Incontinence
Short title	SANS-UUI
Protocol ID	NSM-004
Investigational device	
Name	Neuspera's Implantable Sacral Nerve Stimulation (SNS) System
Description	Miniature wireless midfield powered implanted neurostimulation device for urinary urgency incontinence (UUI).
Indications statement	Neuspera's Implantable SNS System is indicated to treat subjects with UUI who have failed or could not tolerate more conservative treatments.
Sponsor	
Name	Neuspera Medical Inc.
Contact details	Neuspera Medical Inc. 51 Daggett Drive San Jose, CA 95134, USA Telephone: +1 408.612.7570
Investigation centers	
Number of centers	Phase I centers selected by the Sponsor based on interest and ability to complete the sub-study in acceptable timeframe.
Clinical investigation design	
Objective	To determine if stimulating a half-hour per day is effective and acceptable by subjects.
Design	Prospective, multi-center, single-arm study with subjects acting as their own control. Subjects who are currently responders (50% or greater reduction in UUI from baseline) with 2 hours daily stimulation on their most recent study visit will complete a sub-study baseline 72-hour bladder dairy. They will then be asked to reduce to a half-hour daily stimulation for a two-week period. At the end of two weeks, they will complete the 72-hour bladder diary and answer two self-assessment questions, indicating if their therapy was effective and if they are willing to continue with half-hour daily stimulation for another two weeks. This will be repeated for two more weeks (6 weeks total) at which time subjects will exit the sub-study. At the end of the sub-study, subjects will decide which duration of daily stimulation is preferred to use going forward (half-hour or 2 hours).
Follow-up visits	After completing a baseline 72-hour bladder diary, there will be three sub-study visits completed at two-week internals (14 days +/-4). Visits may be completed by telephone or in clinic.
Total duration	Total duration 6 weeks (84 days +/-12)

Endpoints	• Assessment of subjects' satisfaction with half-hour daily simulation compared with 2 hours daily simulation. • Self-assessment of UUI symptoms • 72-hour bladder diary
Safety endpoints	No additional safety endpoints in sub-study. Safety endpoint reported in SAN-UUI main study.
Clinical investigation population	
Sample size	Up to 17 Phase I subjects currently in follow-up may participate.
Inclusion criteria	Only Phase I subjects will be eligible to participate in this study. Eligible participants should meet the following criteria: 1. Provide informed consent for this sub-study, showing their willingness to complete the additional bladder diaries, study questions, and intention to follow the daily stimulation and sub-study requirements. 2. Are responders (50% or greater reduction in UUI from baseline) at the most recent Phase I clinic visit. 3. Have demonstrated consistent use of 2 hours daily stimulation in the last 30 days before sub-study baseline bladder diary. 4. Are currently free from symptoms of urinary tract infection (UTI) or other conditions that could confound UUI symptoms before sub-study baseline bladder diary. 5. Are not experiencing any technical issues with the Neuspera system that would impact receiving stimulation.
Statistical analysis	
Statistical design	Analyses for the sub-study will consist of descriptive statistics since stand-alone definitive conclusions regarding safety or efficacy from this sub-study are not desired, and the purpose of sub-study is to inform on the feasibility of a shorter duration stimulation time. Formal statistical conclusion from this sub-study will not be made so there are no type I error concerns.

1. INTRODUCTION

This is a sub-study addendum to the SANS-UUI Phase I study. The primary objective of Phase I was to assess the utilization of the system during the SNS trial and follow-up periods and to help inform the length of hours of daily stimulation to be used in Phase II of the study. Phase I demonstrated that a short daily stimulation (2 hours per day) with the Neuspera System delivers appropriate urinary urgency incontinence (UUI) symptom relief. Please refer to the SANS-UUI Protocol (NSM-004) for the full details of Phase I design and methods.

1.1. Rationale

The sub-study rationale is to objectively determine if half-hour daily stimulation is effective in satisfactorily addressing UUI. The population to be studied includes subjects from the SANS-UUI Phase I Study who have continued to meet success criteria (50% improvement of UUI episodes) on their most recent 72-hour bladder diaries, and who are interested in the potential to maintain their benefit with a reduced daily stimulation requirement.

During the SANS-UUI study, 2 hours of daily stimulation provided a greater than 50% reduction in UUI episodes in over 90% of the responding subjects; this outcome was similar to outcomes seen with commercially available devices utilizing continuous stimulation 24-hours a day. The SANS-UUI study was not designed to determine if less than 2 hours of daily stimulation could also be successful. There is recent evidence from the Bluewind study 2-year outcomes (John P. F. A. Heesakkers, March 2025)[1] that a tibial nerve stimulation regimen of 30 minutes twice weekly may be effective for subjects initially completing therapy for 1 hour twice a day. Therefore, it seems likely that a reduced stimulation time will be similarly effective for sacral neuromodulation. Subjects will be allowed to return to two-hours a day of stimulation if desired.

2. STUDY DESIGN

2.1. Study Purpose

The purpose of this study is to investigate the effectiveness and subject acceptance of half-hour daily stimulation to treat UUI.

2.2. Objective

To determine if stimulating a half-hour per day is effective and acceptable by subjects.

2.3. Study Design

Prospective, multi-center, single-arm study with subjects acting as their own control.

The sub-study will be implemented with minimal disruption to the SAN-UUI Phase I study. All Phase I subjects are currently past their 48-Month follow-up, and the clinic visit internal is every 6 months. Eligible subjects will complete this sub-study over a 6-week period, between scheduled clinic visits.

Figure 1 shows the study design and subject flowchart. Subjects who are currently responders (50% or greater reduction in UUI from baseline) with 2 hours daily stimulation on their most recent study visit will complete a sub-study baseline 72-hour bladder dairy. They will then be asked to reduce to half-hour daily stimulation for a two-week period. At the end of two weeks, they will complete the 72-hour bladder diary and answer two self-assessment questions, indicating if their therapy was effective and if they are willing to continue with half-hour daily stimulation for another two weeks. This will be repeated for two more weeks (6 weeks total) at which time subjects will exit the sub-study. At the end of the sub-study, subjects will decide which duration of daily stimulation is preferred to use going forward (half-hour or 2 hours).

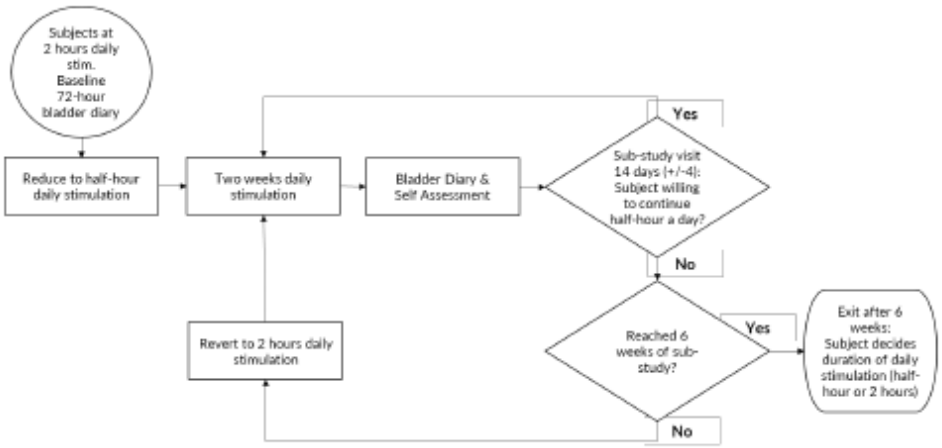

FIGURE 1: SUB-STUDY DESIGN AND SUBJECT FLOWCHART

2.4. Statistical Considerations

Analyses for the sub-study will consist of descriptive statistics since stand-alone definitive conclusions regarding safety or efficacy from this sub-study are not desired, and the purpose of sub-study is to inform on the feasibility of a shorter duration stimulation time. Formal statistical conclusion from this sub-study will not be made so there are no type I error concerns.

2.5. Subjects

Only Phase I subjects will be eligible to participate in this study. Eligible participants should meet the following criteria:

1. Provide informed consent for this sub-study, showing their willingness to complete the additional bladder diaries, study questions, and intention to follow the daily stimulation and sub-study requirements.
2. Are responders (50% or greater reduction in UUI from baseline) at the most recent Phase I clinic visit.
3. Have demonstrated consistent use of 2 hours daily stimulation in the last 30 days before sub-study baseline bladder diary.

4. Are currently free from symptoms of urinary tract infection (UTI) or other conditions that could confound UUI symptoms before sub-study baseline bladder diary.
5. Are not experiencing any technical issues with the Neuspera system that would impact receiving stimulation.

2.6. Procedures

Subjects will complete the sub-study between the scheduled clinic visits in SANS-UUI Phase I, which are completed at 6-month intervals. All the sub-study visits and required assessments below can be completed as Unscheduled Telephone visits or Unscheduled Clinic visits.

2.6.1. Sub-study 72-hour Bladder Diary

Eligible participants are to complete a sub-study baseline 72-hour bladder dairy. Additionally, the 72-hour Bladder Diary will be collected at the end of each two-week stimulation period.
If a 72-hour Bladder Diary was completed for a regular Phase I clinic visit within 14 days of beginning this sub-study and the subject meets the eligibility criteria, that bladder diary can be used as the baseline diary.

2.6.2. Weekly Stimulation Diary

Subjects are to continue to complete the Weekly Stimulation Diary. The diary will be updated to provide the option of half-hour daily stimulation.

2.6.3. Two-Week Stimulation Period

After the sub-study baseline, subjects are to reduce daily stimulation to a half-hour and use for two weeks. At the end of the two-week stimulation period a sub-study visit will occur at 14 days (+/- 4), and subjects are to complete the following items:

1. A 72-Hour Bladder Diary. Voiding volume is not required. The 72-hour bladder dairy should start 7 to 4 days before the sub-study visit.
2. Two self-assessment questions:
    a. Do you feel your UUI symptoms are:
        - ☐ Much worse
        - ☐ A little worse
        - ☐ The same
        - ☐ A little better
        - ☐ Much better
    b. Are you satisfied with the result of half-hour daily stimulation or would you like to resume the previous regimen of 2 hours per day?

Subjects who want to continue with half-hour daily stimulation will continue with another two-week stimulation period and repeat the 72-hour bladder diary and the self-assessment questions noted above at the next sub-study visit.

Subjects who do not want to continue with half-hour daily stimulation will revert to 2 hours daily stimulation; they will continue to complete diaries every two weeks until sub-study completion. If using 2 hours daily stimulation, they do not need to complete the self-assessment questions.

A final two-week stimulation period will be completed, for a total of six weeks. At the end of the final period, subjects will repeat the 72-hour bladder diary and complete the self-assessment questions noted above. At this time, subjects will exit the sub-study and continue with their preferred duration of daily stimulation (half-hour daily stimulation or 2 hours of daily stimulation). For subjects who participate in this sub-study, it will not be considered a protocol deviation in the main study if they use half-hour daily stimulation during or after sub-study participation.

2.6.1. Adverse Events and Changes to Medication

As required in the SANS-UUI main protocol, the following will also be completed and documented in the EDC at each unscheduled sub-study visit (Telephone or Clincal):

- Changes to medication (including OAB medications) and OAB therapies
- Adverse event assessment

2.6.2. Data Collection

Subjects will complete the sub-study with the data collection methods established in the SANS-UUI study, using the ePRO bladder diary, weekly stimulation diary, and the EDC system.

The Unscheduled Follow-up visits in EDC will be used to capture the additional visits (Telephone and/or Clinic) required for the sub-study. The self-assessment questions will be added to the Unscheduled Follow-up visit eCRF.

2.7. Impact on Safety

There are no new impacts on safety with a reduction to half-hour daily stimulation. One potential risk is that half-hour daily stimulation will not be as effective in treating UUI symptoms as 2 hours daily stimulation, and, in this case, subjects may choose to revert to 2 hours daily stimulation.

3. ETHICS AND REPORTING

All the ethical elements and reporting requirements as stated in the SANS-UUI protocol will be followed.

3.1. Written Informed Consent

The Informed Consent Addendum for this sub-study must be approved in writing by an IRB or EC, as applicable. Written Informed Consent must be obtained prior to any sub-study-related procedure. To reduce the burden on subjects, the Informed Consent process can be completed remotely (i.e., by mail and telephone). Each site will follow their process for obtaining and documenting for Informed Consent.

4. REFERENCES

John P. F. A. Heesakkers, P. T.-H. (March 2025). Two-Year Efficacy and Safety Outcomes of the Pivotal OASIS Study Using the Revi System for Treatment of Urgency Urinary. *JOU* , Vol. 213, 323-332.