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STUDY PROTOCOL

Design of a Multicenter, Randomized Controlled Trial for the Treatment of Peripheral Neuropathic Pain (COMFORT Study) with a Micro-Implantable Pulse Generator

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Background: Peripheral Nerve Stimulation (PNS) is an established therapy for chronic neuropathic pain of peripheral origin, typically following nerve injury. However, there is a paucity of Randomized Controlled Trials (RCTs) demonstrating the therapeutic benefits of PNS. The goals of the current study (COMFORT Study) are to document the safety and efficacy of the Nalu Neurostimulation in a PNS RCT, compared to conventional medical management (CMM).

Methods/Design: This is a prospective, multicenter, RCT evaluating the treatment of neuropathic pain with PNS therapy. One of the following four regions will be targeted for treatment: low back, shoulder, knee or foot/ankle. Consented subjects will undergo a baseline evaluation, after which they are randomized 2:1 (PNS+CMM arm to CMM arm). Subjects randomized to PNS+CMM arm will undergo a trial implant period using best clinical practices. Subjects who pass the trial phase, by showing a $\geq$ 50% reduction in pain relative to baseline, will receive the permanent implant. All subjects receiving a permanent implant will be followed for a total of 36 months. At the 3-month primary end point, subjects in CMM arm will be given the option to crossover into PNS+CMM arm, beginning with a trial implant. The study duration is expected to be 5.5 years from first enrollment to last follow-up of last subject and subsequent study closure. Adverse events will be captured throughout the study.

Discussion: The COMFORT study, described here, has the potential to demonstrate the efficacy and safety of the Nalu Neurostimulation System in the treatment of peripheral neuropathy. Results of this study will be the first Level-I evidence, out to 36 months, validating the use of this PNS system in the treatment of chronic pain. This study is designed to enroll the largest cohort, to date, of subjects comparing PNS+CMM vs CMM alone.

Plain Language Summary: Peripheral nerve stimulation (PNS) has been used for decades to treat neuropathic pain of peripheral origin. This therapy typically involves the placement small (~1 mm diameter) cylindrical electrodes (leads) near the nerve(s) in question, which is then followed by the delivery mild electrical pulses to the target, thereby blocking the pain signal from reaching the central nervous system. Despite the clinical success of this approach, there are few randomized controlled trials (RCTs) demonstrating

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PNS efficacy in the treatment of peripheral neuralgia/neuropathy. This may be, in large part, due to a paucity of PNS devices that are small enough to deliver this therapy at multiple locations in the extremities and the torso. For example, most implantable pulse generators (IPGs) range in size from 14 to 40 cm^3 in volume. The purpose of this RCT is to demonstrate the safety and efficacy of an externally powered micro-IPG (<1.5 cm^3 in volume), in the delivery of PNS to treat peripheral neuropathic pain. Active Arm subjects will receive therapy with the micro-IPG and continue to use conventional medical management (CMM); Control Arm subjects will be treated with CMM only. The primary endpoint is the responder rate at 3-months, in both arms, defined as the percentage of subjects with ≥50% pain reduction from baseline following implantation of the micro-IPG. Control Arm subjects will be given the option to crossover to the Active Arm at 3-months. Study subjects in both arms are followed out to 36 months.

Keywords: peripheral nerve stimulation, PNS, chronic pain, neuropathy, neuralgia, micro-IPG, battery-free

Introduction

Conservative therapies are the first line of treatment for chronic peripheral nerve pain syndromes. These include physical, occupational, massage, biofeedback, TENS, topical agents, and behavioral or cognitive therapy. Over-the-counter pain medications round out the first-line treatments. The second-line treatments include nerve blocks through injection of steroids or local anesthetics. Prescription medications such as opioids and/or membrane stabilizers may also be indicated at this stage. The final line of therapies includes more invasive treatments such as peripheral nerve stimulation (PNS), intrathecal drug infusion, or nerve ablation.

Device-based neuromodulation therapies have experienced an impressive expansion of capabilities, which has allowed physicians to successfully treat a wide variety of previously intractable chronic pain ailments.[1] To date, spinal cord stimulation (SCS) has received much of the literature attention. However, despite the expansion of SCS therapies, there remain many neuropathic maladies that may not be responsive to SCS. Furthermore, even in those patients whose peripheral neuropathies may benefit from stimulation of the nervous system upstream of the pain, there always exists the elevated risks associated with epidural access, as well as patient reluctance to receive a spinal implant. Thus, PNS may provide an alternative for the treatment of neuropathic peripheral pathologies that are a bit more downstream and with potentially lower rates of comorbidities.

PNS has been used for decades to treat peripheral neuropathic pain.[2–4] However, the data demonstrating long-term favorable outcomes is primarily limited to retrospective studies.[3,5–7] There is only a handful of prospective studies.[8,9] This is, in large part, due to the large implant size of conventional systems, which were not designed with PNS targets in mind, such as nerves in the limb. The current study design is intended to deliver the first multicenter, prospective, randomized trial evaluating PNS for the treatment of peripheral neuropathic pain with a micro-implantable pulse generator (micro-IPG; <1.5 cc in volume).

Study Goals and Objectives

The primary objective of this study is to document the comparative effectiveness and safety of peripheral nerve stimulation (PNS) plus conventional medical management (CMM) versus CMM alone, in the treatment of chronic, intractable peripheral neuropathic pain.

The secondary objectives are to:

1. Evaluate the comfort, subject compliance, and usability of the wearable components of the Nalu Neurostimulation system.
2. Evaluate subject satisfaction and response to the system with patient reported outcomes (PRO).

Materials and Methods

Trial Design

The study is a prospective, multicenter RCT evaluating the comparative effectiveness and safety of PNS plus CMM versus CMM alone, in the treatment of chronic, intractable peripheral neuropathic pain. Up to 100 subjects will be

randomized 2:1 (PNS+CMM to CMM) at up to 20 centers in the United States (US). The total follow-up period is 36 months, following implant, for all participants. Subjects may choose to cross over from the CMM arm to the PNS+CMM arm, at 3 months. Subjects who do not cross over will be followed for 36 months from randomization. This study was posted on ClinicalTrials.gov with registration number NCT05287373 (February 8, 2022). Institutional Review Board approval was received prior to commencement of study activities.

Participants

Subjects with peripheral neuropathic pain in the knee, low-back, shoulder or foot/ankle, and who have not obtained satisfactory results with CMM will be candidates for study participation. Once informed consent is obtained, subjects will move into the screening phase of the study, which will include a baseline evaluation to ensure inclusion/exclusion criteria are met.

Inclusion Criteria

1. Subject is between 18 and 80 years of age at the time of enrollment.
2. Subject would have been prescribed PNS therapy regardless of participation in this study; the use of the Nalu device must be on-label.
3. Subject has been diagnosed with one or more of the conditions listed below in the low back, shoulder, knee, or foot (including ankle):
   - Post-surgical/post-traumatic peripheral neuropathic pain including but not limited to pain due to peripheral nerve injury, post-surgical scar formation, nerve entrapment.
   - Mononeuropathy, specified or unspecified or in diseases classified elsewhere.
   - Other neuropathy or neuropathic pain.
   - Osteoarthritic pain.
4. Subject has chronic (defined as at least 6-month duration), intractable peripheral neuropathic pain, exclusive of the craniofacial region; any nociceptive pain must be less prominent than the neuropathic pain. Pain should have a predominant neuropathic component as per the investigator's clinical assessment.
5. Subject should have a pain score of at least 6, in the target area of pain, as recorded on the BPI-Q5 (NRS) at screening.
6. Subject is willing to cooperate with the study requirements including compliance with the study procedures and completion of all study visits.
7. Subject reported stable pain (non-escalating) for 60 days prior to signing informed consent.
8. Subject is currently receiving CMM and has had stable pain medication use and dosage for 30 days prior to signing informed consent.
9. Subject is psychologically qualified to receive a peripheral nerve stimulator as per the clinician's standard clinical practice and judgment and does not have clinically relevant psychological condition(s) that would interfere with their ability to accurately report outcomes or complete study procedures.
10. Subject has demonstrated the ability to appropriately place the adhesive clip in the location where the micro-IPG is most likely to be implanted. Alternatively, subject can appropriately use the relief belt and/or limb cuff to keep the Therapy Disc in place.

Exclusion Criteria

1. Subject currently has an active implantable medical device such as a drug pump, spinal cord stimulator, peripheral nerve stimulator, sacral nerve stimulator, deep brain stimulator, and/or cardiac pacemaker.
2. Subject has previously failed PNS, SCS, or Dorsal Root Ganglion (DRG) therapy (trial or permanent implant).
3. Pain is completely absent at rest.
4. Subject has clinical evidence of complex regional pain syndrome (CRPS), peripheral neuralgia or neuropathy of metabolic origin, post-herpetic origin, biochemical evidence of a metabolic or genetic neuropathy (eg, Charcot-Marie-Tooth Disease) or mixed motor/sensory polyneuropathy.

5. Subject has a medical condition that would prevent them from participating in the current study per investigator's or medical monitor's judgment.
6. Subject has had a successful (≥50% pain relief) interventional procedure within the past 3 months to treat the same pain condition(s) being examined in this study, including nerve blocks.
7. Uncontrolled depression or uncontrolled psychiatric disorders.
8. Subject is currently participating in another clinical investigation with an active treatment arm.
9. Subject is allergic or sensitive to materials used in the device components including skin adhesives or does not tolerate the wearable aspect of the device.
10. Subject has pending or ongoing legal issues (including unresolved worker's compensation claims or equivalent) or other conflicting secondary gain issues related to their chronic pain condition.
11. Subject has a current diagnosis of a coagulation disorder, bleeding diathesis, or progressive peripheral vascular disease that has not been medically corrected.
12. Subject has an active systemic infection.
13. Subject is unable to read and/or write in English or give informed consent.
14. Subject has a life expectancy of less than 1 year.
15. Subject has an active malignant neoplasm (metastatic or local) or evidence of paraneoplastic syndrome.
16. Subject with uncontrolled diabetes mellitus, showing signs of diabetic neuropathy, as evidenced by a neurological exam and an HbA1c test.
17. Subject has evidence of an alcohol or drug dependency within the last 6 months prior to enrollment.
18. Subject is pregnant (if female and sexually active, subject must be using a reliable form of birth control, be surgically sterile or be at least 1 year post-menopausal).
19. Subject is nursing/breastfeeding.
20. Subject is on ≥90 mg-morphine equivalents per 24 hours.
21. Subject has undergone an ablative treatment of the target peripheral nerve, or proximal nerve trunk giving rise to the target nerve, or dorsal roots (and DRGs) that ultimately make up the target nerve. No ablative procedures directed at the spinal cord, dorsal roots, or peripheral nerve(s) being treated in the study. To note, subjects who have undergone RF ablation of the dorsal rami, cool pulsed RF of the facet innervation may be considered for enrollment. See note below.

Identification and Description of the PNS Device

The Nalu Neurostimulation System (Nalu Medical, Carlsbad, CA, USA) is the PNS system of choice, which incorporates a battery-free, micro-IPG, powered by an externally worn device –known as a Therapy Disc (TD). The micro-IPG receives radio frequency (RF) power and control data from the TD worn over the micro-IPG site. An adhesive clip applied to the skin or a relief belt, positioned appropriately, holds the TD in place (see Kalia et al[10] for a complete device description). The study sponsor manufacturers the Nalu PNS system, which has US market 510(k) clearance (K183579, K191435) for the treatment of chronic pain originating from peripheral nerves. This study will exclusively use the Nalu PNS system to control for variables that are device-specific.

Indications for Use

The Nalu Neurostimulation System for PNS is indicated for pain management in adults who have severe intractable, chronic pain of peripheral nerve origin, as the sole mitigating agent or as an adjunct to other modes of therapy used in a multidisciplinary approach. The Nalu Neurostimulation System for PNS is not indicated to treat pain in the craniofacial region.

The implant procedure for the Nalu PNS system will follow the on-label implant instructions contained in the FDA-cleared instructions for use (IFU; see also Kalia, et al[10]). These well-established procedures take place in two phases: Trial Implant and Permanent Implant.

Trial Implant: the trial implant phase allows the subject and physician to determine if PNS therapy provides adequate relief, prior to implanting the permanent device. This phase may last up to 30 days, per device labeling, and it begins with

the placement of one or two trial leads, with the aid of fluoroscopy or ultrasound. Paresthesia mapping, during lead placement, will be performed as it is a part of routine care.

Once they are properly placed, the trial leads are percutaneously externalized for post-operative programming, with the goal of providing optimal pain relief. For the purpose of this study, it is anticipated that trials will be completed within 7–10 days. A successful trial is defined as the subject realizing ≥50% pain relief compared to baseline, based on the NRS score from the BPI-Q5. At the end of the trial, the leads are removed. If the trial is successful, the subject is scheduled for permanent implant. If the subject does not have a successful trial, the subject will be given the option to stay in the study, in a secondary CMM control arm, or exit the study.

Permanent Implant: As with standard PNS procedures, the leads are placed in a minimally invasive manner per standard of care and as described in the IFU. The micro-IPG is placed in an accessible region that has been deemed comfortable by the subject and appropriate by the implanting physician. The leads may be placed with the aid of fluoroscopy or ultrasound, based on nerve target and physician preference. Paresthesia mapping will be performed and documented in the OR, prior to confirming the final lead location.

Programming and Activation: Once healed, a sponsor representative will check the device for proper functioning and program the device, under direction of a physician, to optimize pain relief. Subjects will be sent home with Therapy Discs, adhesive clips, a relief belt, and a remote control. Programming details will be captured in the Clinician Programmer.

Patient Reported Outcomes (PROs)

PROs will be used in the study to collect data on pain outcomes (NRS, VAS, BPI, Pain and Paresthesia Maps, Pain Medication Use), Quality of Life (QoL), Activities of Daily Living (ADLs), Mood, overall impression of change as well as comfort of the external wearable. These PROs are collected at all follow-up visits except at 1 month and 9 months.

Pain Outcomes – VAS and BPI-Q5

The Visual Analogue Scale (VAS) and the BPI-Q5 (NRS) are subjective measures of pain.

EuroQol Quality of Life Questionnaire

The EQ-5D-5L is a standardized, validated non-disease-specific measure of health-related quality of life.

Oswestry Disability Index

The Oswestry Disability Index (ODI) is a commonly used outcome-measure questionnaire designed to assess the effects of pain on activities of daily living (ADL).

Brief Pain Inventory

The Brief Pain Inventory (BPI) asks questions about pain relief, pain quality, and the subject's perception of the cause of pain.

Patient Satisfaction

Subjects will be asked to rate their overall satisfaction with the Nalu PNS system using a 5-point Likert scale.

Pain/Paresthesia Maps

Data on the area of pain will be collected by asking subjects to highlight the areas where they are experiencing pain on a body map drawing.

Pain Medication Use

The subject's current pain medication regimen will be documented, including the dose of medication, the number of times per day the medication is taken, and the reason for taking the medication.

Stimulator Usability Questionnaires

Subjects will be asked to record and rate their experience with the wearable components (Therapy Disc, adhesive clip and/or relief belt, and/or limb cuff).

Patient Global Impression of Change (PGIC)

Subjects will be asked to rate their overall global impression of improvement or worsening, if any, in their activity, symptoms, emotions and overall quality of life, since beginning the therapy.

Beck Depression Inventory (BDI)

The Beck Depression Inventory (BDI) is a questionnaire used to assess the severity of depression.

Pain Catastrophizing Score (PCS)

PCS is a questionnaire that characterizes the tendency to magnify the value of the pain.

Primary Effectiveness Hypothesis

The primary effectiveness hypothesis for this study is based upon the responder rate, defined as percent of subjects with ≥50% reduction in NRS for their primary area of pain, captured on the Brief Pain Inventory-Question 5 (BPI-Q5). The null hypothesis is that the responder rate of the subjects with the PNS system is less than or equal to those with CMM alone, at 3 months.

The hypothesis test for the primary effectiveness endpoint is as follows:

$H_{0:}\ \pi_{PNS} \leq \pi_{CMM}$

$H_1: \pi_{PNS} > \pi_{CMM}$

where π_{PNS} is the responder rate for subjects assigned to the PNS system and π_{CMM} is the responder rate for subjects assigned to CMM alone. The test will be based on a two-sample exact binomial test of proportions, at the one-sided 0.025 alpha level. Analysis will be based on evaluable data without imputation for missing data.

Primary Endpoint

The primary effectiveness endpoint is the percentage of responders at 3-months. Responders are defined as subjects with ≥50% reduction in NRS (captured in the BPI-Q5), for their primary area of pain, relative to baseline. Comparisons will be made between randomized arms.

Secondary Endpoints

- Percent change in pain from baseline to 3, 6, 12, 18, 24, 30 and 36 months, for both arms. Comparisons between arms will be made (NRS-BPI-Q5).
- Percentage of responders at 6, 12, 18, 24, 30 and 36 months in both arms (NRS-BPI-SF-Q5).
- Percentage of responders and percent change from baseline, in the cross-over group, at 3, 6, 12, 18, 24, 30 and 36 months post-device activation (NRS-BPI-Q5).
- Change in patient reported outcomes (PGIC, medication use, patient satisfaction, ODI, BDI, EQ-5D, PCS) at 3, 6, 12, 18, 24, 30 and 36 months, in both arms and the cross over arm.
- Comfort, compliance, and usability of the external wearable components at 3, 6, 12, 18, 24, 30 and 36 months, post-device activation, in active arm and cross-over arm.
- Rate of serious and non-serious adverse device events at 3, 6, 9, 12, 18, 24, 30 and 36 months.
- Rate of adverse procedure effects and unanticipated serious adverse device effects at 3, 6, 9 12, 18, 24, 30 and 36 months.

A basic study flow chart is shown in Figure 1. Subjects in both arms will be followed at protocol-specified time points from enrollment to study completion.

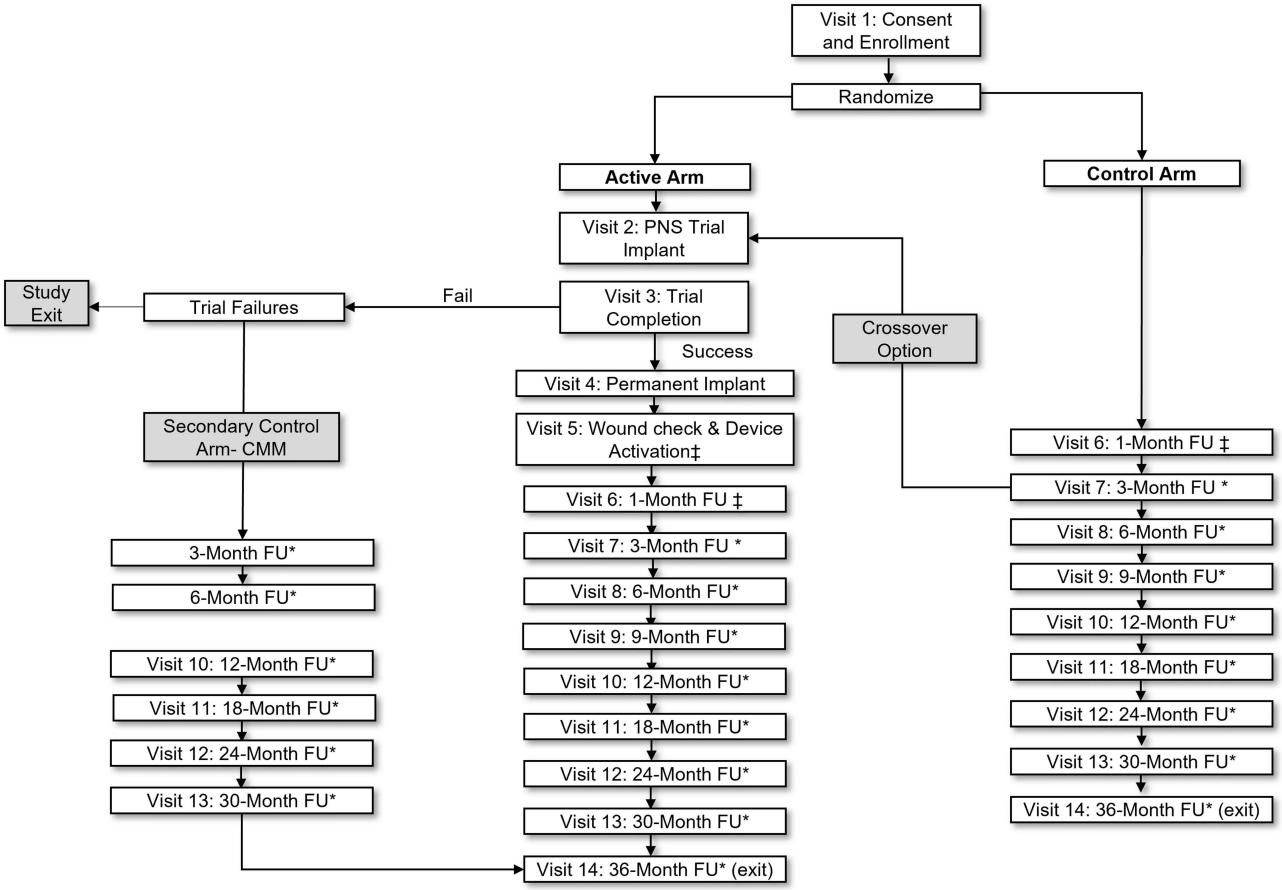

Figure 1 Study flow chart showing the flow of subjects from consent (first study visit) and randomization to 36-month follow-up (last study visit). ‡Phone follow up every 2 weeks; *Phone follow up every 6 weeks; programming visits PRN.

Device Malfunction, Revision, Removal and Replacement

Revision or replacement of leads and/or IPG will be offered to the subject, at the discretion of the clinician. Any subject who requires a revision/replacement of their PNS lead or IPG prior to the 3-month time point will have their study visits restarted (at Visit 4, device implant) based on the date of the new lead/IPG placement. If the subject requires revision/replacement of their trial leads, during the Trial Implant Phase of the study, their study visits will be restarted based on the revision/replacement date (restart at Visit 2).

Conventional Medical Management (CMM)

Subjects in the control arm will be followed at 1-, 3-, 6-, 9-, 12-, 18-, 24-, 30- and 36-months post randomization. Upon randomization, subjects in the control arm will continue to maintain their current conventional medical management regimen for a minimum of 3-months. CMM, defined as the best standard of care for each individual subject, will be determined by the investigator. Below are some common treatments that may be offered to subjects by the investigators:

- Oral medication, including analgesics, NSAIDs, neuromodulating agents, antidepressants
- Topical applications (example, CBD Oils, Lidocaine patches, pain patches, compound creams)
- Physical therapy and rehabilitation
- Psychological management
- Acupressure and acupuncture
- Cognitive behavior therapy
- Nerve Blocks: Nerve blocks may be administered during the study, within the first 6-weeks of enrollment.

- Epidural Steroid Injections (ESI): Epidurals may be administered during the study, within the first 6-weeks of enrollment.
- Transcutaneous electric nerve stimulation (excluded in the PNS+CMM arm)

Cross-Over

At the end of 3-months, subjects in the control arm may be allowed to cross-over and receive a PNS system, if they meet the following 3 criteria: meet all study inclusion/exclusion criteria, have less than 50% pain reduction with current CMM treatment, have investigator approval to cross-over. Subjects who do not meet these 3 criteria will remain in the CMM arm to study completion.

Sample Size Determination

Sample size for the study is based on power requirements for the primary effectiveness endpoint. A total sample size of up to 100 randomized subjects is planned, leading to 90 expected evaluable, based on a 10% attrition rate. An interim analysis will allow for the potential of an early conclusion, provided a large treatment effect.

Randomization

On confirmation of eligibility, subjects will be randomized into one of the two arms, ie, active arm or control arm. Randomization will be performed using a random permuted block design (block size of 3) with a 2:1 allocation ratio (PNS+CMM arm to CMM arm). Randomization will be stratified by investigational site, and treatment allocation will be assigned via a centralized electronic system.

Blinding and Potential Bias

Owing to the nature of the treatments – an implanted device compared to CMM – blinding subjects, investigators, or other study personnel, is not feasible. Therefore, study bias will be reduced in the following ways: randomization, use of CMM in both arms, use of multiple study centers, limiting device use to device-cleared labeling, prospective data collection.

Criteria and Procedures for Subject Withdrawal or Discontinuation

Subjects may be exited from the study for non-treatment-related reasons only when no other option is possible. Reasons for discontinuation include but are not necessarily limited to:

- Voluntary withdrawal from the study by the subject.
- Subject is determined to be lost-to-follow-up.
- Subject is unwilling or unable to cooperate with study requirements (stimulation regimen, follow-up visits, etc.).
- Non-compliance with protocol requirements or device usage.
- Subject has an adverse event or other issue such that they can no longer continue to participate in the study.
- At physician's or medical monitor's discretion.
- Discontinued subjects will not be replaced in the study.

Data Monitoring Plan

Monitoring will be carried out at regular intervals to ensure compliance with the protocol, ISO 14155:2020, Good Clinical Practices (GCP), the Declaration of Helsinki and local regulations. A medical monitor may be used to ensure appropriate subjects are enrolled and to adjudicate the classification of adverse events and other medical issues that arise.

Subgroup Analyses

Subgroup analyses of the primary safety and effectiveness endpoints may be performed for the following subgroups: sex, target nerve/area, and stimulation type. Subgroup analyses will be performed on the primary analysis cohort with complete data. For each subgroup, a logistic regression model will be fit that includes fixed effects for treatment arm, subgroup, and treatment by subgroup interaction.

Interim Analysis

An interim analysis may be performed under a Lan-DeMets implementation of a group sequential design. Type I error for the primary effectiveness endpoint will be controlled via use of an O'Brien-Fleming type alpha-spending function.

Sensitivity Analysis

Sensitivity analysis for the primary safety and effectiveness endpoint will be performed, including multiple imputation to address missing data.

Poolability Analysis

All study sites will follow the requirements of a common protocol and standardized data collection. The primary safety and effectiveness endpoints will be presented separately for each site using descriptive statistics. Poolability of the primary endpoints across investigational sites will be evaluated using a logistic regression model with fixed effects for treatment, site, and treatment by site interaction. The model will be based on subjects in the modified Intent-to-Treat (mITT) population.

Adverse Events, Adverse Device Effects, and Device Deficiencies

Adverse events, adverse device effects, serious adverse events, serious adverse device effects, unanticipated serious adverse device effects, and device deficiencies will all be captured and tallied for each study subject.

Safety Analyses

Adverse events (AEs) will be reported for all enrolled subjects. AEs will be tabulated with the number of events and subjects for each event type and overall. Rates will be reported as the number of subjects who experience at least one event out of the total number of subjects, with follow-up to the beginning of the analysis interval. Rates will be compared between the two study arms. Serious Adverse Events (SAEs) will also be tabulated. All AEs and SAEs will also be summarized by relatedness to the study, the device, and the procedure.

Duration of the Project

The study duration is expected to be 5.5 years from first enrollment to last follow-up of last subject and subsequent study closure.

Ethics, Consent and Confidentiality

The study and each site will be approved by an Institutional Review Board prior to commencement of study enrollment. Written, IRB-approved informed consent will be obtained from each subject before commencing any study-related activities, including data collection. Confidentiality of participant data will be maintained, at all times, by each individual involved in the study.

Discussion

The first PNS surgery was performed on a 26-year-old woman with clinical presentation consistent with a complex regional pain syndrome.[11] This implant activated the ulnar and medial nerves, in the arm, and induced a "pleasant tingling in the lateral three fingers and corresponding hand and stopped the pain …." Since this first highly experimental application of PNS, the field has evolved considerably.

Modern developments in PNS therapy tend to be centered on the reduction of invasiveness and mitigation of surgical trauma. When compared to implantation of SCS systems in the low back or abdomen, there is significantly less room for traditional IPGs to be implanted in the extremities, without causing pocket pain, erosion, or discomfort. When IPG size becomes prohibitive, in terms of implant locations outside the torso, the leads may need to be tunneled extensively and across joints to the IPG, which could result in lead migration and/or breakage, not to mention added surgical trauma. Thus, there is a notable need for smaller implantable devices where extremities are concerned.

Despite the published benefits of PNS therapy in treating peripheral mononeuropathies,[8,9] there exists a lack of well-designed PNS studies, as well as a distinct lack of PNS device choices. When the apparent benefits of PNS are taken into account, the need for more in-depth and rigorous evaluations of PNS devices becomes clear. Although PNS involves the implantation of a medical device, it is a minimally invasive, reversible surgery. Complications are usually mild and resolve quickly. In particular, the Nalu micro-IPG (~1.5 cc in volume) lends itself towards minimally invasive techniques and procedures. The Nalu PNS system allows for either four or eight electrode contacts on single or dual leads, combined with a micro-IPG. A trial implant period of up to 30 days, with a multitude of electrode configurations and therapy options is available for both the trial and the permanent system.

Limitations

This is an RCT; unfortunately, it is not possible to blind this study given the disparities between treatments. The PNS +CMM study arm includes a surgical procedure followed by daily subject interaction with the implanted device, for proper functioning. The CMM arm has no such surgery nor device associated with the therapy.

Data Sharing Plan

The authors do not intend to share any data beyond what is included in the manuscript. The published data from this study are available in Hatheway et al (2024).[12]

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Disclosure

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