STATISTICAL ANALYSIS PLAN
for the
SENZA-PDN-1 Study

A Post-Market, Multicenter, Prospective, Randomized Clinical Trial Comparing 10 kHz Spinal Cord Stimulation (HF10™ Therapy) Combined with Conventional Medical Management to Conventional Medical Management Alone in the Treatment of Chronic, Intractable, Neuropathic Limb Pain

Investigational Plan: CA2016-5 US SENZA-PDN-1

Sponsor: Nevro Corp.
1800 Bridge Parkway
Redwood City, CA 94065

Version 3.0

September 15, 2019

DOCUMENT HISTORY

Revision	Description	Date
1.0	Original Version	September 15, 2017
2.0	Revisions for compatibility with Protocol Version D	April 25, 2019
3.0	Organization and Analysis Details for Previously Specified Secondary, Tertiary, and Exploratory Endpoints	September 15, 2019

SIGNATURE PAGE

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A. INTRODUCTION

The purpose of this post-market study is to document comparative safety, clinical effectiveness, and cost-effectiveness of the addition of HF10™ therapy to CMM compared with CMM alone in subjects with chronic, intractable, neuropathic lower limb pain due to diabetic neuropathy (Painful Diabetic Neuropathy or PDN). This study is a multi-center, prospective, randomized comparison of the two treatments.

The Senza® Spinal Cord Stimulation (SCS) system (manufactured by Nevro Corp., Redwood City, CA) is a Food and Drug Administration (FDA) approved device system (PMA P130022) indicated as an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with failed back surgery syndrome, intractable low back pain and leg pain. The system is designed to deliver electrical stimulation to the spinal cord using electrodes (also referred to as leads) and implantable pulse generators (IPGs) as described in this investigational plan. Conventional medical management (CMM) may include a variety of non-invasive or minimally invasive treatments that comprise the standard of care for neuropathic limb pain. The study interventions are to be used in accordance with Institutional Review Board (IRB) approval and require informed consent from study subjects.

A list of the abbreviations used in the description of the study can be found in the Appendix.

B. DEVICE DESCRIPTION

The Senza System is a totally implantable spinal cord stimulation system that is intended to aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain, and leg pain, and received CE Mark in May 2010, Therapeutic Goods Administration (TGA) approval in Australia in June 2011, and FDA PMA approval in May 2015. The Senza System is similar to other commercially available SCS systems in design and function.

The Senza System consists of a rechargeable implantable pulse generator (IPG) with 16 output channels. The IPG is implanted in a subcutaneous pocket and is capable of stimulating the spinal cord nerves when used with one or two 8-contact percutaneous leads. The IPG is controlled by a Patient Remote and/or the Programmer.

Other components of the system include an external Trial Stimulator capable of delivering the same stimulation as the IPG, Lead, Extensions, Charger and charging system, operating room (OR) cables and surgical accessories.

C. STUDY POPULATION

C.1 Indications for Use

HF10 therapy **(**Senza System PMA P130022) has been approved by the FDA with Indications for Use including the management of neuropathic pain of the limbs as described in the Investigational Plan. Treatment of subjects with peripheral neuropathies that result in limb pain is therefore an on-label use of the Senza System. CMM will follow the Investigators' standard of care and/or published clinical guidelines. Treatments include, but are not limited to, pharmacological agents, physical therapy, cognitive therapy, chiropractic care, nerve blocks, and other non-invasive or minimally invasive therapies.

C.2 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for study participants are indicated below.

C.2.1 Inclusion Criteria

To participate in the study, subjects must meet all of the following inclusion criteria:

1. Have been clinically diagnosed with diabetes, according to the American Diabetes Association guidelines, as well as painful diabetic neuropathy (PDN) of the lower limbs, and:
   a. are symptomatic despite conservative therapy for a minimum of 12 months
   b. have tried pregabalin (Lyrica®) OR gabapentin (Neurontin®, Gralise®, administered at an adequate dose and for an appropriate duration, in the Investigator's judgement
   c. have tried at least one other class of analgesic medication in addition to pregabalin/gabapentin
   d. are on a stable dosage of analgesic medications for at least 30 days
2. Average pain intensity of ≥ 5 out of 10 cm on the VAS in the lower extremities at enrollment.
3. Have stable neurological status measured by motor, sensory and reflex function as determined by the investigator.
4. Be on a stable analgesic regimen, as determined by the Investigator, for at least 30 days prior to assessing pain intensity as described in inclusion criterion #2, and be willing to stay on those medications with no dose adjustments until activation of the permanently implanted SCS device (HF10 therapy group) or baseline assessment (CMM only group).
5. Be 22 years of age or older at the time of enrollment.
6. Be an appropriate candidate for the surgical procedures required in this study based on the clinical judgment of the implanting physician.
7. Be capable of subjective evaluation, able to read and understand English-written questionnaires, and able to read, understand and sign the written informed consent in English.
8. Be willing and capable of giving informed consent.
9. Be willing and able to comply with study-related requirements, procedures, and scheduled visits.
10. Have adequate cognitive ability to use a patient programmer and recharger as determined by the Investigator.

C.2.2 Exclusion Criteria

To participate in the study, subjects must *not* meet any of the following exclusion criteria:

1. Have a diagnosis of a lower limb mononeuropathy (e.g., causalgia and tibial or peroneal neuropathies), have had a lower limb amputation other than toes due to diabetes, or have large (≥3 cm) and/or gangrenous ulcers of the lower limbs.
2. Have an average pain intensity of ≥ 3 out of 10 cm on the VAS in the upper extremities due to diabetic neuropathy at enrollment.
3. Currently have a hemoglobin A1c (HbA_{1c}) > 10%.
4. Have a BMI > 45.
5. Currently prescribed a daily opioid dosage > 120 mg morphine equivalents.

6. Have a medical condition or pain in other area(s), not intended to be treated in this study, that could interfere with study procedures, accurate pain reporting, and/or confound evaluation of study endpoints, as determined by the Investigator (such as primary headache, fibromyalgia, post-herpetic neuralgia, osteoarthritis, peripheral vascular disease, or small vessel disease).
7. Have a current diagnosis of a progressive neurological disease such a multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, rapidly progressive arachnoiditis, brain or spinal cord tumor, central deafferentation syndrome, Complex Regional Pain Syndrome, acute herniating disc, severe spinal stenosis and brachial plexus injury, as determined by the Investigator.
8. Have a current diagnosis or condition such as a coagulation disorder, bleeding diathesis, platelet dysfunction, low platelet count, severely diminished functional capacity due to underlying cardiac/pulmonary disease, symptomatic uncontrolled hypertension, progressive peripheral vascular disease or uncontrolled diabetes mellitus that presents excess risk for performing the procedure, as determined clinically by the Investigator.
9. Have prior experience SCS, dorsal root ganglion (DRG) stimulation, peripheral nerve field stimulation (PNfS), or peripheral nerve stimulation (PNS) trials for chronic intractable pain.
10. Have significant spinal stenosis, objective evidence of epidural scarring and/or any signs or symptoms of myelopathy as determined by MRI conducted within the past 12 months.
11. Any previous history of surgery on the posterior elements (laminectomy, posterior fusion) resulting in a compromised epidural space, as determined by the Investigator.
12. Be benefitting from an interventional procedure and/or surgery to treat lower limb pain (Subjects should be enrolled at least 30 days from last benefit).
13. Have an existing drug pump and/or another active implantable device such as a pacemaker.
14. Have a condition currently requiring or likely to require the use of diathermy or MRI that is inconsistent with Senza system guidelines in the Physician's Manual.
15. Have either a metastatic malignant neoplasm or untreated local malignant neoplasm.
16. Have a life expectancy of less than one year.
17. Have a local infection at the anticipated surgical entry site or an active systemic infection.
18. Be pregnant or plan to become pregnant during the study. Women of childbearing potential who are sexually active must use a reliable form of birth control, be surgically sterile, or be at least 2 years post-menopausal.
19. Have within 6 months of enrollment a significant untreated addiction to dependency producing medications, alcohol or illicit drugs.
20. Be concomitantly participating in another clinical study.
21. Be involved in an injury claim under current litigation.
22. Be a recipient of Social Security Disability Insurance (SSDI) benefits due to chronic pain.
23. Have a pending or approved worker's compensation claim.
24. Have evidence of an active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, compliance with intervention and/or ability to evaluate treatment outcome, as determined by a psychologist in the last 12 months.

D. STUDY DESIGN

This is a post-market, multi-center, prospective, randomized clinical study to document the comparative safety, clinical effectiveness, and cost-effectiveness of the addition of HF10 therapy to CMM compared with CMM alone in subjects with chronic, intractable, neuropathic lower limb pain. Data from follow-up visits will be compared to baseline data for each treatment group. Comparisons will also be made between the treatment groups. A single interim analysis for purposes of adaptive sample size re-estimation is planned.

D.1 Primary Objective

The ***primary objective*** of this post-market study is:

To compare the safety, clinical effectiveness, and cost-effectiveness of HF10 therapy plus CMM to CMM alone for the treatment of chronic, intractable, neuropathic lower limb pain resulting from diabetic neuropathy.

D.2 Success Criteria

The primary endpoint of this study is a composite of safety and effectiveness, specifically the difference between treatment groups in responder rates at 3-month follow-up in subjects without a clinically meaningful neurological deficit compared with baseline.

Individual subject success encompasses clinical effectiveness and safety at the 3-month follow-up:

- Effectiveness: A responder is defined as a subject with ≥ 50% improvement from baseline lower limb pain score, as measured by the 10 cm VAS. For each subject, the right and left lower limb VAS scores collected during a single visit will be averaged to generate the lower limb pain score.
- Safety: A subject without a clinically meaningful decrease from baseline in neurological status.

Study success is assessed by comparing responder and safety rates between treatment groups at 3 months.

D.3 Randomization

Following completion of the Baseline procedures, eligible subjects will be randomized at sites, with blocking within sites to achieve a 1:1 ratio to either the HF10 therapy plus CMM group or CMM alone in four strata: A1c (<7%, ≥7%) x pain severity (VAS <7.5cm, ≥7.5cm). Those randomized to the stimulation group will receive HF10 therapy with the Senza System in addition to CMM.

D.4 Blinding

This study is not blinded. Due to the nature of the treatments, specifically an implanted medical device compared with CMM, it is not feasible to blind either the subjects or the clinical site personnel to the treatment group assignments. It is believed that responses provided by subjects or Investigators / clinical staff will not be significantly impacted by the knowledge of which treatment is received. The sponsor and study participants, however, will be blinded to ongoing or aggregate results of the study, except for recommendations regarding sample size re-estimation arising out of a single pre-planned interim analysis.

D.5 Crossover

Subjects randomized to either treatment group will have the potential to crossover to the alternative treatment arm at the 6-month visit if they meet all of the following criteria:

- < 50% lower limb pain relief from baseline. For pain relief calculations, a subject's right and left lower limb VAS scores collected during a single visit will be averaged together to generate a lower limb pain score.
- Documented subject dissatisfaction with the treatment ("dissatisfied" or "very dissatisfied" on subject satisfaction measure).
- Investigator agreement with crossover

D.6 Duration

The expected duration of this study is approximately 52 months. Enrollment is expected to last 20 months, with subjects followed up to a 24-month period following permanent implant (HF10 therapy plus CMM group) or baseline assessment (CMM only group), with a composite of effectiveness and safety assessed at 3 months post-intervention. Due to the crossover option included in the study design, the time commitment for an individual subject to complete the study will vary from approximately 26 months to 32 months, consisting of Baseline assessments, up to 14 days of trial stimulation followed by permanent device implant for subjects randomized to the device arm, and last follow-up at 24 months post-intervention.

D.7 Sample Size

A total of 97 evaluable subjects per study group (total of 194) would be required to compare the primary endpoint between groups, based on an assumed 60% responder rate for the HF10 therapy group (80% trial success rate and 75% responders at 3 months among permanent implant subjects) and a 36% responder rate for the CMM only group, with 90% power, and two-sided type I error of 0.05.

Up to 432 subjects will be provisionally enrolled at multiple clinical sites in the United States. Assuming a 50% screen failure rate, an estimated total of 216 subjects will be randomized, resulting in 108 subjects assigned to each treatment group. The subjects will continue with their respective treatments through the 3-month primary endpoint assessment with an expected 10% attrition rate, resulting in approximately the 97 evaluable subjects (108 x 90%) in each group required for evaluation of the primary endpoint. An interim analysis will be performed to reassess sample size assumptions when 25% of the subjects reach the 3-month primary endpoint.

E. PROTOCOL

Subjects who participate in this study will undergo evaluations that include entry criteria qualification, baseline assessments, trial stimulation (HF10 therapy subjects), and post-trial assessments (HF10 therapy subjects). Subjects randomized to the HF10 therapy plus CMM arm with a successful trial phase will be eligible to receive a permanent implant of an IPG and leads. Subjects randomized to the CMM only arm will be optimized according to the Investigator's standard of care and/or clinical treatment guidelines. Subjects will receive their assigned treatment for 24 months with assessments at 1, 3, 6, 9, 12, 18, and 24 months Post-Intervention.

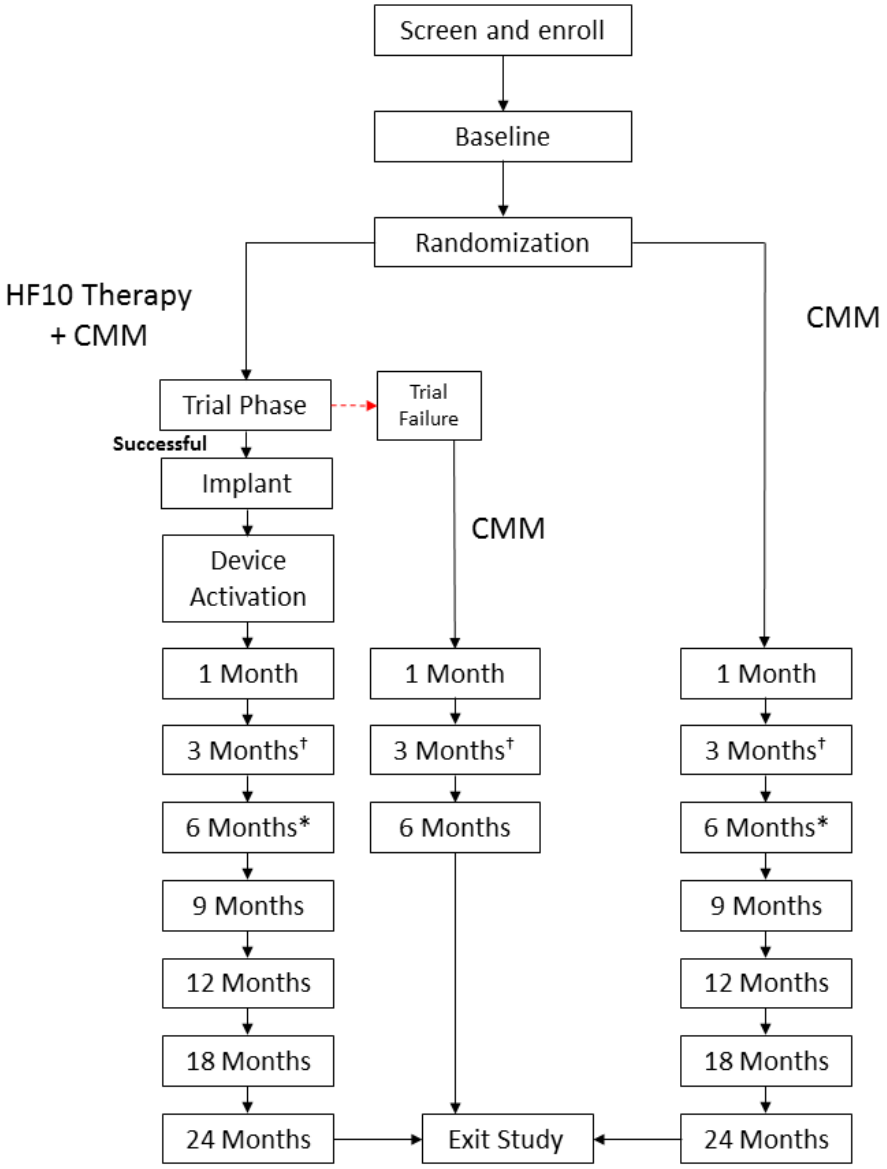
Randomized subjects will undergo a Trial Phase lasting up to 14 days to determine his/her response to SCS therapy. Following the Trial Phase with external device stimulation, subjects will be assessed for their pain. Those who have an "unsuccessful" trial with less than 50% lower limb pain reduction from baseline will be followed on CMM for 6 months prior to study completion. Those who have a "successful" Trial Phase (defined as a 50% or greater pain reduction in lower limb pain from Baseline) will be eligible to proceed to permanent implantation of a Senza system. Following permanent device implant, the IPG will be activated and stimulation will be delivered on an ongoing basis for the entirety of the patient's participation in the study, up to 24 months. At the 6-month assessment, subjects may opt to crossover to the CMM only treatment arm if they meet the criteria for crossover. Subjects who crossover will complete the remainder of the scheduled 24 months of follow-up.

The follow-up schedule for the CMM only group starts at the baseline assessment and will continue up to 24 months. Subjects may opt to crossover to the HF10 therapy plus CMM group at the 6-month assessment if they meet the criteria for crossover. These subjects will undergo trial stimulation with HF10 therapy with those who achieve at least 50% lower limb pain reduction from baseline eligible for a permanent device

implant. Permanent implant subjects will receive 24 months of stimulation delivery with regularly scheduled assessments. Subjects who crossover to the HF10 therapy arm but fail trial stimulation with less than 50% lower limb pain reduction from baseline will be monitored for adverse events for 2 weeks before exiting the study.

A summary of the study milestones can be seen in Figure 1 and a summary of assessments can be found in Table 1.

Figure 1. Summary of the sequence of study-related assessments, procedures, and activities.



†Primary endpoint analysis
*Option to cross-over to other therapy arm

Table 1: Schedule of Assessments	Enrollment			Trial & Permanent Phase (SCS only)				Follow-up Phase						
Visit	Consent	Entry Criteria	Baseline Assessment	Trial Implant	End of Trial (EoT)	Permanent Implant	Device Activation (DA)	1 Month Visit	3 Month Visit	6 Month Visit	9 Month Visit	12 Month Visit	18 Month Visit	24 Month Visit
Window	-			-	0-14 d from Trial Implant	0-60 d from EoT	0-14 d from Perm. Implant	4 wks ± 7 d from DA (SCS) or baseline (CMM)	12 wks ± 14 d from DA (SCS) or baseline (CMM)	24 wks ± 30 d from DA (SCS) or baseline (CMM)	36 wks ± 30 d from DA (SCS) or baseline (CMM)	52 wks ± 30 d from DA (SCS) or baseline (CMM)	78 wks ± 30 d from DA (SCS) or baseline (CMM)	104 wks ± 30 d from DA (SCS) or baseline (CMM)
Informed Consent	X													
Medication Usage		X[b]	X	X	X	X	X	X	X	X	X	X	X	X
Diabetes Medication Usage			X	X	X	X	X	X	X	X	X	X	X	X
Healthcare Utilization			X					X	X	X	X	X	X	X
Pain Assessment (VAS)		X	X		X			X	X	X	X	X	X	X
Weight		X	X						X	X		X		X
Pregnancy Test		X[c]												
Psychological Evaluation		X[d]												
Medical/Surgical History		X												
MRI		X[e]												
AP/Lateral and/or Oblique X-Rays[f]				X	X	X		[X]	[X]	[X]	[X]	[X]	[X]	[X]
Neuropathic Pain Assessment (DN4)			X		X			X	X	X		X		X
Modified Neuropathy Sym Score (NSS)			X		X			X	X	X		X		X
Brief Pain Inventory (BPI-DPN)			X					X	X	X	X	X	X	X
Pain Experience (SF-MPQ-2)			X						X	X		X		X
Diabetes Quality of Life (DQOL)			X						X	X		X		X
Quality of Life Assessment (EQ-5D-5L)			X						X	X		X		X
Pain and Sleep Assessment (PSQ-3)			X					X	X	X	X	X	X	X
Pt Global Impression of Change (PGIC)									X	X		X		X
Clin Glob Impression of Change (CGIC)									X	X		X		X
Assessment of Functioning (GAF)			X					X	X	X	X	X	X	X
6-Minute Walk Test (6MWT)			X						X			X		X
Labwork		X							X	X		X	X	X
Subject Satisfaction									X	X		X		X
Neurological Assessment			X		X				X	X		X		X
Work Status & Disability			X							X		X		X
Third-Party Payer Data			X											
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X
Wound Assessment			X				X	X	X	X	X	X	X	X
Device Programming[f]				X		X	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
Paresthesia Assessment[f, g]				[X]	[X]	[X]	[X]	[X]	X	[X]	[X]	[X]	[X]	X
Pain Map[f]				X	X				X	X		X		X
Additional Symptom Map[f]				[X]		[X]			X	X		X		X
Crossover										[X]				
Study Completion[h]				[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	X

[a]All Entry Criteria to be completed before the Baseline Assessment. [b]Pain medications must be stable for ≥30 days before VAS may be completed. [c]To be completed for participants of child bearing potential. [d]Psychological evaluation to be completed for subjects who did not have an evaluation performed within the last 12 months. [e]MRI to be completed for subjects who did not have one within the last 12 months. [f]For SCS subjects only. [g]May be performed as appropriate, as determined by the field clinical engineer. [h]To be completed for all subjects upon completion of the study, including those who withdraw early or do not pass the Trial Phase. Trial failure subjects who were initially randomized to SCS will be followed for 6 months while subjects who fail trial after crossover will be followed for a minimum of 2 weeks or until resolution of an ongoing adverse event, if applicable, prior to completing this form. Wks = weeks, d = days, [X] = optional

F. STATISTICAL ANALYSES OF STUDY ENDPOINTS

This section contains the details of the statistical analyses to be performed on data collected during the study, including the pre-specified study endpoints.

F.1 General Considerations

1. Descriptive statistics will be used to summarize all subject Baseline and outcome data collected during the study. Continuous variables will be summarized using means, standard deviations, medians, and ranges. Categorical variables will be summarized in frequency distributions.
2. Statistical analyses will be performed by validated software (e.g., SAS, IBM/SPSS, or Cytel Software)
3. Statistical tests appropriate to the endpoint being examined will be used and identified. Parametric tests (e.g., Student's t-tests) will be utilized, if the distributional properties of the data are suitable. If parametric tests are not indicated, the associated non-parametric tests (e.g., Mann-Whitney tests, Fisher's Exact Tests) will be used.
4. A two-sided p-value of 0.05 or less for the primary endpoint will be considered evidence of statistical significance. Reported p-values for all other tests will be considered nominal and unadjusted for multiple testing, without conclusions regarding statistical significance levels.
5. Copies of databases used to prepare clinical report summaries will be archived to enable any statistical analyses performed to be replicated.
6. A full data listing will be prepared, including an electronic version in a standard computer-accessible format (e.g., SAS) at the completion of the study. Listings of data represented on the case report forms (eCRF) will be provided for all key baseline, demographic and outcome variables to facilitate further investigation of tabulated values and to allow for clinical review of safety variables.

F.2 Analysis Populations

The following analysis populations are defined for the study:

Intention-to-Treat (ITT): All subjects randomized into the CMM and CMM+HF10 study groups. This is considered the Safety Population for purposes of reporting on any reported adverse events.

Per Protocol (PP): All randomized subjects who are either randomized into the CMM group or are randomized to the CMM+HF10 group and receive a SENZA System implant, and who complete the 3-month primary assessment.

F.3 Data Collection

Data will be collected using eCRFs via an Electronic Data Capture (EDC) system (M-Core, Medrio Inc.). Data will be entered directly into eCRFs in the EDC system at the sites. The clinical site will record data on outcome variables as well as adverse events should they occur. Subject confidentiality will be maintained and each subject will be identified by his or her subject number. Subject names will not be published. Study data to be collected is summarized in **Error! Reference source not found.**.

F.4 Study Endpoints

The following effectiveness and safety endpoints will be evaluated during the study.

F.4.1 Effectiveness

Primary Endpoint

The primary endpoint of this study is a composite of safety and effectiveness, specifically the difference between treatment groups in responder rates at 3-month follow-up in subjects without a clinically meaningful neurological deficit compared with baseline. A responder is defined as a subject

with ≥ 50% lower limb pain reduction from baseline. For each subject, the right and left lower limb VAS scores collected during a single visit will be averaged together to generate a lower limb pain score.

Analysis: The primary analysis population for this endpoint is the ITT population. A secondary analysis will be performed in the PP population. The responder rates will be compared between groups with a Fisher's Exact Test.

In addition to the primary endpoint, multiple secondary and tertiary endpoints will be evaluated. For all analyses, right and left lower limb VAS scores collected on a single visit will be averaged together to generate a lower limb pain score for each subject. The primary analysis population for secondary and tertiary endpoints is the PP population.

Hierarchically Tested Secondary Endpoints

If the primary endpoint is found to be statistically significant at an alpha level of 0.05, then the following secondary endpoints will be successively tested in the order shown with the same two-sided alpha level of 0.05 until statistical significance cannot be demonstrated:

1. Difference between the treatment groups in proportion of subjects with a lower limb pain VAS score ≤ 3.0 cm at 3 months.
2. Difference between the treatment groups in crossover rates.
3. Difference between the treatment groups in responder rates at 6 months.
4. Difference between the treatment groups in the proportion of remitters (remission is defined as having a lower limb pain VAS score of ≤ 3.0 cm for at least 6 months) at 6 months.
5. Difference between the treatment groups in the proportion of subjects with overall improvement from baseline in neurological assessment (motor, sensory, reflex) at 3 months.
6. Difference between the treatment groups in the proportion of subjects with overall improvement from baseline in neurological assessment (motor, sensory, reflex) at 6 months.
7. Difference between the treatment groups in changes in health-related quality of life as assessed by the EuroQol Five Dimensions questionnaire (EQ-5D-5L) at 6 months.
8. Difference between the treatment groups in the average percentage change from baseline in HbA_{1c} levels at 6 months.

Analyses:

Secondary endpoints 1-6 will be tested using a Fisher's Exact Test for differences in proportions or rates.

Secondary endpoints 7-8 will be testing using two-group Student's t-tests.

Tertiary Endpoints

The following tertiary endpoints will be summarized using descriptive statistics appropriate to the specific endpoints but not formally tested for statistical significance. Results of statistical testing may be reported, but any p-values will be considered nominal and unadjusted for multiple testing without conclusions regarding significance levels.

- Difference between the treatment groups in the average percentage change from baseline in lower limb pain VAS scores at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.

- Difference between the treatment groups in proportion of subjects with ≥ 30% improvement in lower limb pain VAS at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.
- Within group evaluation of proportion of remitters at 12 and 24 months.
- Within group evaluation of responder rates at 12 and 24 months.
- Within group evaluation of proportion of subjects with improvement from baseline in neurological assessment (motor, sensory or reflex) at 12 and 24 months.
- Difference between the treatment groups in Numbers Needed to Treat (NNT) based on responder rates at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups in average percentage change from baseline in opioid dosage at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups in average percentage change from baseline in PDN-specific analgesic dosages at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups in average percentage change from baseline in HbA_{1c} levels at 3 months. Within group evaluation will be done at 12 and 24 months.
- Difference between the treatment groups in average percentage change from baseline in diabetic control medication dosages at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups in average percentage change from baseline in BMI at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups in the average percentage change from baseline on distance covered during the 6MWT at 3 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups in the change over time in size of any baseline lower limb wounds at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups at 3 and 6 months in health economic outcomes, including: 1) healthcare utilization [i.e. medications, office visits, ER visits, hospital admissions, medical tests, etc.]; 2) employment status; and 3) health-related quality of life as assessed by the EuroQol Five Dimensions questionnaire (EQ-5D-5L) and the Diabetes Quality of Life measure (DQOL). Within group evaluations will be done at 12 and 24 months.

Additional details concerning specific instruments to be evaluated are provided below:

Douleur Neuropathique 4 (DN4): DN4 is a well validated survey to help identify subjects with neuropathic pain. The questionnaire has 10 yes/no items that describe qualities of pain as well as assess the presence of sensory nerve phenomena such as hypoesthesia and allodynia.

Modified Neuropathy Symptom Score (NSS): The modified NSS is a 5-item questionnaire with a maximum score of 9 that evaluates symptoms of neuropathy in the lower limbs.

Paresthesia assessment: Representatives of Nevro may record where subjects experience paresthesia with the SCS system at low (non-therapeutic) frequency. Summary results, if available, will be presented.

Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN): The BPI-DPN is a modified version of the Short Form BPI, a brief survey that assesses the severity of the subject's pain and the level of interference with typical life activities, such as sleeping, walking, and working. The BPI-DPN has been validated in patients with PDN.

McGill Pain Questionnaire: The Short Form McGill Pain Questionnaire version 2 (SF-MPQ-2, hereafter referred to as MPQ) is a well validated and widely used questionnaire used to measure the major symptoms of pain. Subjects will be asked to rate the intensity of each of 22 pain descriptors from 0 (do not experience, or none) to 10 (worst possible) at follow-up visits outlined in the schedule of events.

Four subscale scores (continuous pain, intermittent pain, predominantly neuropathic pain, and affective descriptors) and a total score will be calculated. Each subject's baseline scores will be compared to the scores at study visits. Mean change from baseline will be calculated for the entire cohort.

Diabetes Quality of Life Measure (DQOL): The DQOL is a patient-completed questionnaire with 46 items that ask the respondent to select a value of 1 to 5, with 1 representing "no impact," "no worries," and "always satisfied," while a score of 5 represents "always affected," "always worried," and "never satisfied." The measure was specifically developed and validated in diabetic patient populations. The total score can be broken down into four subscales: satisfaction, impact, diabetes worry, and social worry. A lower score indicates a better quality of life.

EuroQol Five Dimensions Questionnaire (EQ-5D-5L): The EQ-5D-5L is a standardized quality of life questionnaire applicable to a wide range of health conditions. The questionnaire consists of 5 items as well as a health-related VAS and is completed by the subject.

Pain and Sleep Questionnaire Three-Item Index (PSQ-3): Pain and Sleep Questionnaire (PSQ), an eight-item questionnaire developed to assess the impact of pain on sleep. PSQ-3 is a subset of PSQ, consisting of questions 1, 4 and 5 and has been validated to assess impact of chronic pain on sleep.

Medication usage: Medication usage will be recorded at all study visits. Changes of usage for subjects will be summarized.

Healthcare Utilization: Doctors' office visits, ER visits, medical tests, and hospital admissions will be recorded at all follow-up visits.

Global Assessment of Functioning: Investigators will complete a Global Assessment of Functioning (GAF) scale to rate subjectively the social, occupational, and psychological functioning of subjects. This is a numeric scale, with scores of 0 through 100, with 100 being the highest functioning. Mean scores and changes from baseline will be calculated. A higher score indicates an improvement.

Global Impression of Change: Both the subject and clinician will complete a global impression of change scale. This 7-point scale is used to assess the subject's global change in activity, limitations, symptoms, emotions and overall quality of life since the beginning of the study. Responses range from "no change (or condition has got worse)" to "a great deal better". Summary results will be presented for both the subject and clinician completed scales.

Subject Satisfaction Questionnaire: Subject satisfaction will be assessed using a 5-point scale. Responses range from "very satisfied" to "very dissatisfied." Summary results will be presented.

F.4.2 Safety

Safety will be assessed by characterizing clinically meaningful deficits in neurological status (primary) and adverse events (secondary) at all study visits.

Neurologic status includes motor, sensory and reflex functions, which will be characterized as improved, maintained, or a deficit as compared with baseline status

All AEs, SAEs, and UADEs occurring during the study will be collected. The site will document onset, severity, treatment/intervention provided, relationship to the treatment/procedure, and resolution and record the data on the Adverse Event eCRF. Any UADEs and/or deaths occurring during the study procedures will also be evaluated to determine whether the SCS system or medication might have caused or contributed to the event.

The Investigators shall categorize all adverse events for seriousness, severity, and relationship. All determinations of severity, device relation, and resolution are made by the Investigator and not by the Sponsor.

For purposes of consistent adverse event reporting and analysis, adverse events will be categorized using the Medical Dictionary for Regulatory Activities (MedDRA®) terminology, consistent with the *MedDRA® Term Selection: Points to Consider* document. Events are grouped by System Organ Classification (SOC) and Preferred Term (PT), according to diagnosis and/or event description as provided by the Investigator on the eCRF.

Analysis: Summary descriptive tables of events (numbers of events using MedDRA categories, numbers of subjects with events in MedDRA categories) will be reported. Details of SAEs (e.g., description, onset, severity, relatedness to study, resolution or status date, actions taken) will also be provided.

The subject rates of SAEs, and their associated exact 95% confidence intervals, will be estimated for the two treatment groups.

F.5 Interim Analysis

A single interim analysis will be performed to reassess sample size assumptions for evaluation of the primary study endpoint when 25% of the subjects have completed the 3-month primary assessment. This interim analysis will be performed by an independent third party, and knowledge of specific study results will be kept blinded from the sponsor and other study participants. The interim analysis will evaluate the conditional power to detect a significant difference at the completion of the study between treatment groups, given the available 3-month data. A recommendation regarding sample size will be made to the sponsor based on the estimated conditional power:

1. Conditional power $\leq 20\%$: very unfavorable, stop the study early for futility

2. Conditional power > 20% and ≤ 40%: unfavorable, but no increase in sample size
3. Conditional power > 40% and ≤ 80%: promising, increase the sample size by an estimated amount to restore the original design power level of 90%
4. Conditional power > 80%: favorable, but no increase in sample size

The above conditional power intervals result in three possible recommendations that may be made to the sponsor: stopping early for futility, no change in sample size, and increasing the sample size. The sponsor reserves the right to accept or reject any of these recommendations.

A recommendation for no change in sample size associated with "unfavorable" or "favorable" interim results helps ensure the blinding of the actual results. A recommendation to increase the sample size signifies "promising" results, but the results may be in a relatively wide conditional power interval (40% - 80%), and are, similarly, not revealed.

Since there is no provision for stopping the study early on the basis of positive interim findings, there is no impact on the final alpha level (two-sided, alpha = 0.05) for the evaluation of the primary endpoint.

F.6 Missing Data

Since the primary analysis of the primary study endpoint at 3 months will be in the ITT population, a sensitivity analysis will be performed to examine the impact of any missing data on the observed results. This sensitivity analysis will use the multiple imputation method for estimating missing primary endpoint data, based on available baseline and 1-month follow-up data.

All other analyses of secondary and tertiary endpoints will be based on the Per Protocol (PP) population and available data.

F.7 Subgroup Analyses

The following subgroup results for the primary study endpoint will be examined:

- Results at the 3-month primary assessment in the subgroup randomized to CMM + HF10 but who failed the trial phase and were followed for 6 months under CMM therapy
- Follow-up results in those subjects who crossed over to the other treatment group after the initial 6-month visit

Additional exploratory analyses may be performed to examine the consistency of results in selected subgroups (e.g., based on gender, study site, age, pain duration, pain severity, glycemic control, etc.). These analyses may also take the form of multivariable analyses, where the contributions from membership in multiple subgroups to a study endpoint are simultaneously estimated.

F.7 Minimization of Bias

In preparing the investigational plan and associated documentation, an attempt has been made to anticipate and minimize potential sources of bias.

- The qualifications of each Investigator and his/her ability to appropriately screen and treat subjects from his/her caseloads and to comply with investigational plan requirements will be reviewed before their participation in the trial.
- The study will be conducted under a common protocol at all study sites.

- The sponsor and study participants will remain blinded to ongoing or aggregated study results, except for recommendations made concerning sample size re-estimation during a single, pre-planned interim analysis.

APPENDIX: List of Abbreviations

Abbreviation	Definition
6MWT	6-Minute Walk Test
AE	Adverse Event
BPI-DPN	Brief Pain Inventory for Diabetic Peripheral Neuropathy
CE	Conformité Européene (European Conformity)
cGCP	Current Good Clinical Practice
CGIC	Clinician Global Impression of Change
cm	Centimeter
CMM	Conventional Medical Management
CT	Computed Tomography
d	Day
DA	Device Activation
DN4	Douleur Neuropathique 4
DQOL	Diabetes Quality of Life Measure
DRG	Dorsal Root Ganglion
eCRF	Electronic Case Report Form
EMI	Electromagnetic Interference
EoT	End of Trial
EQ-5D-5L	EuroQol Five Dimensions Questionnaire
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric Acid
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
GIC	Global Impression of Change
HbA_{1c}	Hemoglobin A1c
HF10™ therapy	Nevro Senza® 10 kHz Spinal Cord Stimulation
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
ITT	Intention-to-Treat Population
kHz	Kilohertz
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
MHz	Megahertz
min	Minute
mL	Milliliter
mm	Millimeter
MRI	Magnetic Resonance Imaging
NNH	Numbers Needed to Harm
NNT	Numbers Needed to Treat
NSS	Modified Neuropathy Symptom Score

OR	Operating Room
PDN	Painful Diabetic Neuropathy
PGIC	Patient Global Impression of Change
PMA	Premarket Approval
PNS	Peripheral Nerve Stimulation
PP	Per Protocol Population
PSQ-3	Pain and Sleep Questionnaire Three-Item Index
SAE	Serious Adverse Event
SCS	Spinal Cord Stimulation
SF-12	12-Item Short Form Survey
SF-MPQ-2	Short Form McGill Pain Questionnaire
TGA	Therapeutic Goods Administration
TSM	Trial Stimulator
UADE	Unanticipated Adverse Device Effect
VAS	10 cm Visual Analog Scale
wks	Weeks