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Evaluating pain and neurological function with high frequency 10 kHz spinal cord stimulation in the treatment of painful diabetic neuropathy: design of a multicentre, randomised controlled trial (PDN-Sensory)

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ABSTRACT

Introduction Current pharmacological treatment options for painful diabetic neuropathy (PDN) often fail to provide adequate pain relief. However, in the recent SENZA-PDN study, high-frequency 10 kHz spinal cord stimulation (SCS) demonstrated significant long-term improvements in lower limb pain and health-related quality of life (HRQoL) in a PDN population. Furthermore, more than half of 10 kHz SCS recipients showed improved sensory function based on non-blinded clinical assessments in post hoc analysis. We report the design of the PDN-Sensory study, which aims to evaluate changes in pain and neurological function with 10 kHz SCS in the treatment of PDN. The study will include objective measures of neurological function, including the modified Toronto Clinical Neuropathy Score (mTCNS) and intraepidermal nerve fibre density (IENFD).

Methods and analysis This multicentre, prospective, randomised controlled trial will compare conventional medical management (CMM) with 10 kHz SCS+CMM in individuals with diabetes and chronic, intractable lower limb pain due to PDN. Participants will be randomised 1:1 to CMM alone or 10 kHz SCS+CMM, with optional crossover at 6 months. The primary outcome is the proportion of participants at 6 months achieving ≥50% pain relief from baseline. The key secondary endpoint is the proportion of participants at 6 months with a reduction in mTCNS of ≥3 points from baseline (excluding changes in foot pain). Additional endpoints at 6 and 12 months include changes from baseline in mTCNS, IENFD, 7-day averaged pain score, pain-related interference, HRQoL, sleep, psychological outcomes, functional status and metabolic parameters.

Ethics and dissemination The study protocol received central approval from the Western Institutional Review Board (IRB #20230954). Local IRB approval will be required before initiation of the study at each participating clinical site. The study complies with Good Clinical Practice guidelines (ISO 14155), the Declaration of Helsinki, and all applicable national, federal and local regulatory requirements. Dissemination plans include presentations at national and international conferences and publication in a peer-reviewed journal with open access.

Trial registration number NCT05777317.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The first randomised controlled trial aiming to provide objective evidence of the effects of 10 kHz spinal cord stimulation (SCS) on neurological function along with pain relief in patients with peripheral diabetic neuropathy (PDN). The study was carefully designed by leading experts in the field of diabetic peripheral neuropathy.
⇒ A comprehensive set of validated quantifiable patient-reported outcomes aligning with the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials recommendations will be investigated.
⇒ Pragmatic participant selection criteria consistent with current SCS coverage policies for wider real-world adoption of SCS therapy.
⇒ A novel approach via blinded neurological assessments and objective biomarker evaluations will provide unbiased clinical insights into the effects of 10 kHz SCS.
⇒ The absence of an active control group precludes direct comparison between SCS modalities and may be a limitation of this study.

INTRODUCTION

Neuropathy is a common and complex complication of diabetes.[1] The most common phenotype, diabetic peripheral neuropathy (DPN), affects more than half of people with diabetes.[1 2] The condition typically begins with a loss of sensation in the feet, gradually ascending into the lower legs as the disease progresses.[1 2] Individuals with DPN

frequently report numbness in the feet, muscular weakness in the lower extremities and balance impairment, all of which contribute to an increased likelihood of falls and fractures.[3 4] One of the most distressing and debilitating symptoms of DPN is neuropathic pain, experienced by 20%–68% of individuals with the condition.[5 6] Painful diabetic neuropathy (PDN) is characterised by burning, lancinating, shooting and electric shock-like sensations, which can be unremitting, severely affecting sleep and overall quality of life.[1 2]

Current clinical guidelines recommend a multifactorial approach to managing PDN symptoms, involving a combination of oral pain medications, topical therapies (eg, capsaicin 8% patch) and various lifestyle interventions.[1 2] Although oral pharmacological treatments such as pregabalin, gabapentin, duloxetine and amitriptyline are commonly prescribed, they are frequently ineffective and are often poorly tolerated.[7 8] As a result, there has been increasing interest in spinal cord stimulation (SCS) as an alternative therapy for managing PDN pain symptoms.[1]

Traditional low-frequency SCS (LF-SCS) has demonstrated modest effectiveness in alleviating lower limb pain in PDN in a long-term evaluation of two prospective cohorts comprising 40 implanted patients.[9 10] At 2 years, the combined cohort reported an average reduction in pain of 38.8% (n=35).[9] In a subgroup with extended follow-up over 8–10 years (n=19), an average of 55.6% of patients maintained clinically meaningful pain relief (≥30% reduction from baseline).[10] However, despite improved pain scores at 8–10 years, no gains were observed in health-related quality of life (HRQoL) parameters.[10] Additionally, traditional LF-SCS relies on stimulation-generated paraesthesia—an overlapping tingling and/or prickling sensation—which can be uncomfortable or bothersome for some patients with PDN already burdened by disease-induced paraesthesia.

In contrast, high-frequency 10 kHz SCS provides pain relief without inducing paraesthesia. A recent study of the therapy in a PDN population (SENZA-PDN study) demonstrated substantial benefits in recipients of 10 kHz SCS, with an average reduction in lower limb pain of 79.9% after 2 years of treatment.[11] Additionally, a real-world, post-study survey, with a mean follow-up of 4.1 years post-implantation, later found that 76.8% of respondents reported clinically meaningful pain relief with 10 kHz SCS, accompanied by a significant improvement in HRQoL.[12] Notably, the SENZA-PDN study revealed a clinically meaningful improvement in neurological function in 65.7% of 10 kHz SCS recipients at the 2-year mark, including improvements in sensory function, motor strength and reflexes in the lower limbs.[11 13] This potentially disease-modifying effect is important, given the risk of falls, fractures, foot ulceration and lower limb amputation associated with DPN.[1 14–17] Post hoc subgroup analyses at 2 years also suggested potential metabolic benefits with 10 kHz SCS, indicated by clinically significant reductions in glycated haemoglobin A1c (HbA1c) and weight among those with type 2 diabetes and elevated pre-implantation HbA1c (>7% and >8%) and body mass index (≥30 kg/m^2 and ≥35 kg/m^2), respectively.[18]

Recent pilot studies suggest that 10 kHz SCS may improve sensory function and promote nerve fibre regeneration in patients with PDN. Chen *et al* observed significantly increased odds of normal pinprick sensory response at 12 months compared with baseline, along with significantly increased proximal and distal intraepidermal nerve fibre density (IENFD) over the same time frame.[19] Kissoon *et al* demonstrated significant reductions at 12 months compared with baseline in lower limb weakness symptoms and positive sensory symptoms such as paraesthesia.[20]

While pain in PDN has often been attributed to peripheral manifestations of the disease, for example, chronic inflammation, peripheral nerve dysfunction and metabolic compromise,[1] recent research has explored the role of central sensitisation in diabetes. Worthington *et al* demonstrated that people with diabetes (type 1 or type 2) and chronic pain exhibited reduced spinal inhibitory tone.[21] Spinal inhibitory tone is believed to play an important role in innocuous sensory processing, particularly in acuity (eg, two-point discrimination) and fidelity (eg, lateral inhibition).[22 23] In a recent study of rodent models of PDN, 10 kHz SCS was seen to normalise the receptive field and amplify weakened vibration and warm neural signals within the spinal cord.[24] Since 10 kHz SCS is thought to work by selectively driving GABAergic inhibitory interneurons in the spinal dorsal horn, the use of 10 kHz SCS may not only reduce pain signalling but potentially improve sensory function by normalising spinal inhibitory tone.[25]

Based on these promising findings, a larger, controlled study was designed to confirm the effects of 10 kHz SCS on neurological function and further elucidate the underlying mechanism of action as a potential disease-modifying therapy. Accordingly, the PDN-Sensory study is a multicentre, prospective, randomised, controlled clinical trial that evaluates the effects of 10 kHz SCS on pain and neurological function in individuals with diabetes and chronic, intractable lower limb pain due to PDN. The study will use validated, objective neurological endpoint measures, including the modified Toronto Clinical Neuropathy Score (mTCNS) and IENFD. This is the first study in the SCS field to include these measures of neurological function as prespecified statistically tested endpoints. Additionally, the study will collect complementary outcomes to assess the wider effectiveness of the therapy on pain-related interference, HRQoL, sleep, psychological outcomes, functional status and metabolic parameters.

METHODS AND ANALYSIS

Objective

The PDN-Sensory study is a multicentre, prospective, randomised controlled trial (RCT) with optional

crossover. It aims to evaluate the effect of 10 kHz SCS on pain and neurological function in individuals with diabetes and chronic, intractable lower limb pain due to PDN.

Study sites

Patients will be recruited at 13 study sites in the USA, including investigators with interventional pain management and endocrinology specialties (see online supplemental table S1 for the full site list).

Ethics

The Western Institutional Review Board (IRB) granted central approval for the study protocol, associated documents and informed consent form (IRB #20230954). Each participating site must obtain additional local IRB approval before initiating enrolment. The study will adhere to Good Clinical Practice guidelines (ISO 14155), the Declaration of Helsinki, and all applicable national, federal and local regulatory requirements. The study is registered at ClinicalTrials.gov (NCT05777317). The study started in April 2023, with expected completion in March 2026.

Eligibility criteria

Potential participants will undergo comprehensive screening after relevant IRB approvals and the provision of written informed consent. Eligibility is determined based on predefined inclusion and exclusion criteria (box 1). Key eligibility criteria include a diagnosis of diabetes according to established American Diabetes Association criteria,[26] presence of PDN as confirmed by an mTCNS>5 (including >2 on sensory examination findings), PDN of the lower limbs for >12 months, neuropathic pain in the lower limbs with intensity ≥5 cm measured on a Visual Analogue Scale (VAS; 0–10 cm) and prior treatment with a gabapentinoid and at least one other class of analgesic, resulting in insufficient pain relief or intolerable side effects. The presence of upper limb pain due to PDN of ≥3 cm (0–10 cm VAS) is an exclusion criterion.

Screening assessments will include pain evaluation, neurological examination, psychological assessment, laboratory tests (including HbA1c and other risk factors), medical record and history review, standardised assessment tools, participant interviews and investigator clinical judgement.

Allocation

Eligible participants meeting all the inclusion criteria and none of the exclusion criteria will undergo baseline assessments before being randomised by the sites using concealed assignment and a block technique in a 1:1 ratio to receive either conventional medical management (CMM) alone or 10 kHz SCS plus CMM (10 kHz SCS+CMM). Randomisation will also be stratified by baseline pain intensity (VAS<7.5 cm vs ≥7.5 cm) and mTCNS (<13 vs ≥13, a published severe peripheral neuropathy threshold value).[27] Randomisation assignments will be

Box 1 Inclusion and exclusion criteria

Inclusion criteria

1. Has been clinically diagnosed with diabetes, according to the American Diabetes Association guidelines, as well as painful diabetic neuropathy (PDN) of the lower limbs.
2. Has a pain intensity (over the last 7 days) of ≥5 out of 10 cm on the Visual Analogue Scale (VAS) in the lower limbs at both the enrolment and baseline visits.
3. Has PDN symptoms that have been present for ≥12 months.
4. Is currently taking or has tried in the past a gabapentinoid and at least one other class of analgesic with insufficient pain relief or intolerable side effects.
5. Has been 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 number 2.
6. Has painful diabetic sensorimotor polyneuropathy confirmed by modified Toronto Clinical Neuropathy Score >5 at enrolment. The total score must include presence of foot pain (≥1) and sensory examination findings (≥2).
7. Has haemoglobin A1c ≤10% as measured at enrolment.
8. Is 22 years of age or older at the time of enrolment.
9. Is an appropriate candidate for the surgical procedures required in this study based on the clinical judgement of the study physician.
10. Is willing to and capable of giving written informed consent.
11. Is willing and able to comply with study-related requirements and procedures and attend all scheduled visits.

Exclusion criteria

1. Has a diagnosis of a lower limb mononeuropathy (eg, causalgia and tibial or peroneal neuropathies), has had a lower limb amputation other than toes due to diabetes, or has large (≥3 cm) and/or gangrenous ulcers or an active infection of the lower limbs at enrolment.
2. Has an average pain intensity of ≥3 out of 10 cm on the VAS in the upper limbs due to diabetic neuropathy at enrolment.
3. Has a history of glycaemia-related hospitalisations or emergency ward visits including ketoacidosis, hyperosmolar state and severe hypoglycaemia in the previous 6 months.
4. Uses anticoagulants or antiplatelet agents that cannot be temporarily discontinued prior to the procedure.
5. Has unstable cardiovascular disease, including untreated cardiac arrhythmias, myocardial infarction within the last 12 months, New York Heart Association functional class III or IV heart failure.
6. Is currently prescribed a daily opioid dosage >120 mg morphine equivalents.
7. Has a medical condition or diagnosis that is inconsistent with the Senza System guidelines in the physician's manual or as per standard clinical practice.
8. Has 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).
9. Has prior experience with spinal cord stimulation, dorsal root ganglion stimulation, peripheral nerve field stimulation or peripheral nerve stimulation for chronic intractable pain.
10. Has an existing drug pump and/or another active implantable device such as a pacemaker (ok to have an insulin pump or continuous glucose monitor that remains externalised).

Continued

Box 1 Continued

11. Has 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.
12. Has a life expectancy of less than 1 year.
13. Has a local infection at the anticipated surgical entry site or an active systemic infection.
14. Is pregnant or plans to become pregnant during the study (participants of childbearing potential that are sexually active must use a reliable form of birth control).
15. Has had within 6 months of enrolment a significant untreated addiction to dependency-producing medications, alcohol or illicit drugs.
16. Is concomitantly participating in another interventional clinical study.
17. Is involved in an injury claim for study-related chronic pain that is under current litigation.
18. Is a recipient of temporary Social Security Disability Insurance benefits due to study-related chronic pain.
19. Has a pending or approved worker's compensation claim for study-related chronic pain.
20. Has 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 investigator in the last 12 months.
21. Has a body mass index >45 at enrolment.

computer-generated and allocated via an electronic data capture system.

The study participant flow is shown in figure 1. A crossover option is available at 6 months for all randomised participants who meet specific criteria: inadequate pain relief (<50% reduction in lower limb pain from baseline), documented treatment dissatisfaction and investigator agreement.

Given the nature of the treatments (ie, device implantation vs CMM), it is impossible to blind study participants and clinical site personnel to the treatment allocation. However, independent clinicians blinded to participant treatment assignments will conduct all the neurological function tests to mitigate potential bias in these assessments. Additionally, participants will be asked not to disclose their treatment assignment to the assessing clinician during these tests.

Interventions

Participants initially randomised to receive 10 kHz SCS+CMM will undergo a temporary stimulation trial for up to 14 days to assess therapy response. During the trial, percutaneous leads will be placed in the epidural space and connected to an external pulse generator, with stimulation parameters optimised to maximise pain relief. Participants who experience a reduction in lower limb pain of at least 50% during the trial period (ie, a successful trial) will proceed to permanent implantation of a 10 kHz SCS system (Nevro, Redwood City, California, USA), subject to the agreement of both the participant and investigator. Participants from the CMM-alone arm who meet the criteria for crossover at 6 months will only proceed to permanent implantation after a successful temporary stimulation trial and the agreement of the participant and investigator.

All participants receiving a permanent 10 kHz SCS system will be followed for 12 months post-implantation. Participants initially assigned to 10 kHz SCS+CMM who fail the temporary stimulation trial will continue within the study for an additional 6 months with CMM. Crossover participants from the CMM-alone arm who fail the stimulation trial will undergo a 2-week adverse event (AE) monitoring period before exiting the study. Throughout the study, both treatment groups will continue to receive CMM per the treating care team's standard practice and/or clinical treatment guidelines for PDN and diabetes.[28]

Participant timeline

Study data will be collected at screening, baseline, 6 months and 12 months, with a subset of measures collected at 3 months and other time points (see online supplemental file 1 for a full schedule of assessments). Study participants will be compensated for time and transportation costs for each visit. Withdrawals from the study and reasons will be recorded in the study database. If a participant randomised to 10 kHz SCS+CMM fails the temporary trial, they will be followed at 3 months and 6 months with all outcomes collected.

Outcome measures

The primary endpoint of the study is the proportion of participants responding to treatment at 6 months, with treatment response defined as a reduction in lower limb neuropathic pain of ≥50% from baseline.[29] The key secondary endpoint is the proportion of participants at 6 months with a decrease in mTCNS of ≥3 points from baseline (excluding changes in foot pain). Other secondary and tertiary outcome measures will include changes from baseline in mTCNS, IENFD, a 7-day average daily pain score, pain-related interference, HRQoL, sleep, psychological outcomes, functional status and metabolic parameters.

Peripheral neuropathy outcome measures

Neurological function

Neurological function will be assessed at baseline, 6 months and 12 months by an independent clinician blinded to the participant's treatment allocation. The same clinician will complete all tests for an individual participant to minimise inter-rater variability. The mTCNS instrument will be used to grade the severity of neuropathy symptoms (foot pain, numbness, tingling, weakness, ataxia and upper limb symptoms) and sensory responses (pinprick, cold temperature, light touch, vibration and position sense in the lower limbs).[27] Each item will be graded from 0 to 3 (maximum score: 33 points). For the mTCNS effectiveness endpoint, the foot pain component will be excluded (maximum score: 30 points) in order to

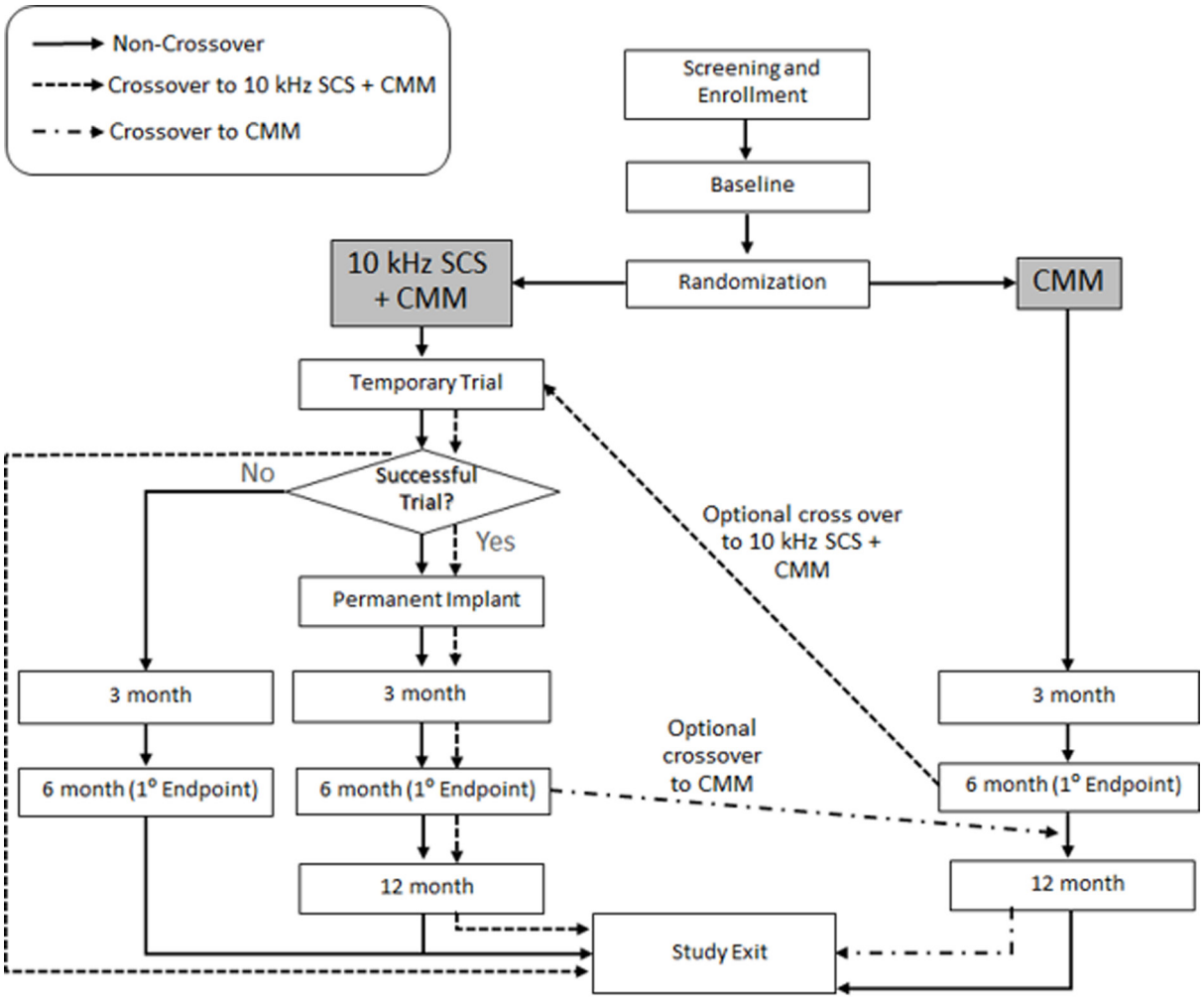


Figure 1 PDN-Sensory study design. The study will randomise an expected 118 participants, with optional crossover at 6 months. CMM, conventional medical management; PDN, painful diabetic neuropathy; SCS, spinal cord stimulation.

isolate this assessment to sensory function other than pain, since pain is already assessed via the primary endpoint of the study. Achilles reflexes will also be tested bilaterally, and two-point discrimination testing will assess the participant's ability to perceive two closely spaced stimuli presented simultaneously on the dominant lower limb. The independent clinician will also complete a blinding assessment (as per Bang *et al*[30]), with a blinding index calculated for each treatment group and time point.

Small fibre neuropathy outcome measure

In line with guidance from the European Federation of Neurological Societies (EFNS) for IENFD measurement,[31] trained site personnel will collect 3 mm punch skin biopsies at two sites on the participant's dominant limb: the lateral lower calf (10 cm proximal to the lateral malleolus) and the lateral upper thigh (20 cm distal to the iliac spine at the level of the pubis). The samples will be sent to a centralised laboratory for analysis and IENFD quantification.

Table 2 and table 2 provide further details of the peripheral neuropathy outcome measures. Patient-reported outcome measures.

A battery of patient-reported outcome measures will evaluate the participant's treatment experience.

Pain and pain interference

Lower limb pain intensity will be measured using a 0–10 cm VAS, averaging scores from the left and right sides. The 11-item Brief Pain Inventory for Diabetic Peripheral Neuropathy will assess diabetes-related pain severity and its interference with daily life (0–10 points scale).[32]

Health-related and neuropathy-related quality of life

The EuroQol 5-Dimensional 5-Level (EQ-5D-5L) questionnaire will assess five generic health dimensions to generate a single index score ranging from less than 0 to 1 (1=full health).[33] The 12-item Short Form Health Survey will measure generic HRQoL to yield a Physical Component Summary score and a Mental Component Summary score (0–100 points).[34] The Neuropathy-Specific Quality of Life Questionnaire will rate six health dimensions specific to diabetic peripheral neuropathy (1–5 points scale): pain and paraesthesia, symptoms of reduced/lost sensation in the feet, unsteadiness while standing/

Table 1 Assessments of peripheral neuropathy

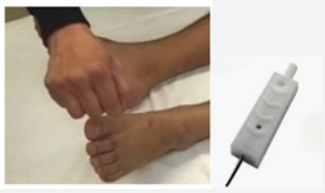
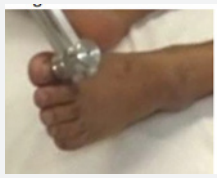
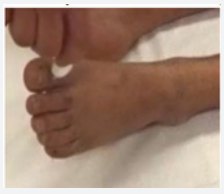
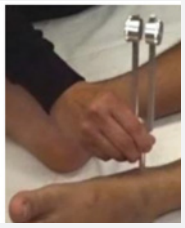
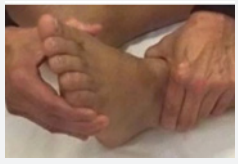
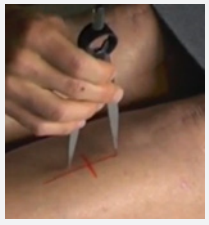
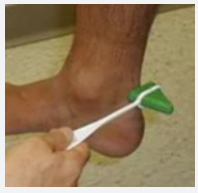
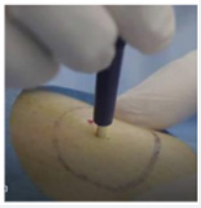
Pinprick	Ability to sense sharp/thinly myelinated A-delta fibres	
Cold temperature	Ability to sense temperature/ thinly myelinated A-delta fibres	
Light touch	Sensitivity to light touch/ thickly myelinated A-beta	
Vibration	Ability to feel vibrations with the use of a tuning fork/thickly myelinated A-beta	
Position sense in the lower limbs	Ability to sense the position of a body part with the eyes closed/thickly myelinated A-beta	
Two-point discrimination	Ability to perceive differences between one or two points of touch	
Reflex	Testing motor function, myelinated A-alpha	
Nerve biopsy	Density of intraepidermal nerve fibres	

Table 2 Items and scoring for the mTCNS endpoint measure*

Neuropathic symptom ► Foot pain ► Numbness ► Tingling ► Weakness ► Ataxia ► Upper limb symptoms	**Scoring** Each of the six neuropathic symptoms is assessed and scored on a scale from 0 to 3: 0=absent 1=present, but no interference with sense of well-being or activities of daily living 2=present, interferes with sense of well-being but not activities of daily living 3=present and interferes with both senses of well-being and activities of daily living (both)
Sensory response ► Pinprick ► Cold temperature ► Light touch ► Vibration ► Position sense in the lower limbs	**Scoring** Each of the five sensory responses is assessed and scored on a scale from 0 to 3: 0=normal 1=reduced at the toes only 2=reduced to a level above the toes, but only up to the ankles 3=Reduced to a level above the ankles and/or absent at the toes

*All neuropathic symptom and sensory response scores will be summed to provide a total mTCNS score for each assessment (maximum score of 33, where a higher score indicates greater severity of neuropathy). For the primary effectiveness endpoint, the mTCNS score will exclude the foot pain score (a maximum score of 30).
mTCNS, modified Toronto Clinical Neuropathy Score.

walking, limitation in daily activities, interpersonal problems and emotional distress.[35]

Sleep

The Pain and Sleep Questionnaire 3-item index will evaluate the impact of chronic pain on sleep onset and maintenance (0–10 cm VAS),[36] and the 7-item Insomnia Severity Index will assess insomnia severity (0–4 points scale).[37]

Psychological assessments

The 9-item Patient Health Questionnaire will measure depression severity (0–3 points scale),[38] and the 16-item Falls Efficacy Scale-International instrument will evaluate fear of falling during various activities of daily living (1–4 points scale).[39]

Work status and disability

A proprietary questionnaire will assess participants' current employment situation, with additional payer and health funding information collected at baseline.

Satisfaction and impression of change

Participants will rate treatment satisfaction using a 5-point Likert scale and their overall perception of change with the 7-point Patient Global Impression of Change scale. Investigators will also rate their impression of change in

the participant's condition using the 7-point Clinician Global Impression of Change scale.

PDN symptom characteristics

Participants will complete lower limb symptom diagrams to represent their pain and PDN symptom distributions. A separate questionnaire will assess several aspects of participants' PDN sensation experience using a 10-point scale.

Other outcome measures

Physical function

The TUG (Timed 'Up & Go') test will assess balance and functional mobility, measuring the time a participant takes to stand up from a chair, walk 3 m, turn, walk back and sit down again.[40] The average of two measurements will be used in analyses.

Metabolic parameters

HbA1c will be measured using standard laboratory tests. Study personnel will record weight.

Medication usage: details of medications used for PDN management and glucose control will be recorded, along with the average daily medication usage over the past 7 days.

Safety

Participants will be monitored for AEs from enrolment through study completion.

Data and safety monitoring

Participant safety will be ensured by noting that the consent was properly documented, the study protocol was followed and that AEs were reported and followed-up as appropriate.

Participants will be assessed for AEs starting at enrolment and continuing through study completion. If an AE occurs, an AE electronic case report form (eCRF) will be completed for all serious AE and any non-serious AEs determined by the investigator to be device-related or procedure-related. The event will be followed until resolution or determination that the participant's condition is stable. The medical specialists shall categorise all AEs for seriousness, severity and relationship. All determinations of severity, device relation and resolution are made by the medical specialist and not by the sponsor. The studied intervention (10 kHz SCS) is US Food and Drug Administration (FDA)-approved and commercially available for the PDN indication. Therefore, a safety monitoring board is not required.

Amendments may be initiated by the sponsor or at the request of the site study team, and all investigators and trial registry will be notified.

Data management

Site personnel will collect data and enter it directly into eCRFs stored in a secure central database maintained by the sponsor. Some eCRFs will be available as electronic patient-reported outcomes (ePRO) assessments. These ePROs will be entered directly into the database by the participant using a tablet device. Participants will be identified solely by their study ID number.

To ensure the quality of the data collected, site quality assurance practices and clinical trial standard operating procedures will be evaluated as part of site qualification and during monitoring visits by the sponsor's clinical monitors. During monitoring visits, source documents will be used to verify information submitted on the eCRFs. Clinical monitoring will include review and resolution of missing or inconsistent results to assure the accuracy of the reported data. Where any discrepancies are noted, they will be resolved with the investigator and/or an individual designated by the investigator. Where the data is incomplete, attempts will be made to obtain the missing data. The source documents will remain at the clinical sites.

The results of monitoring visits will be summarised in written reports, identifying any repeated data problems with the site study personnel and specifying recommendations for resolution of noted deficiencies. The conduct and monitoring of the clinical study will be conducted in accordance with the monitoring plan which requires monitoring of at least 80% of all data.

Patient and public involvement

Neither patients nor the public were involved in the design of the study. The outcome measures were developed by a scientific advisory committee in conjunction with the sponsor, in line with the recommendations from the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT).[41] Patients were not involved in the recruitment and conduct of the study, nor were they asked to assess the burden of the intervention or the time required to participate in the research. Participants may be informed of the final study results by contacting the principal investigator at their site. The outcomes of the study may help in enhancing patient and public involvement.

Statistical analysis

Study endpoints

Primary and secondary study endpoints are listed in box 2. Tertiary endpoints are presented in online supplemental table S3. For the primary endpoint, we will compare the proportion of responders between groups, with treatment response defined as a reduction in lower limb pain of ≥50% from baseline. The analysis will use the modified intent-to-treat population, comprising all randomised participants assigned to CMM alone or those assigned to 10 kHz SCS+CMM who initiate the SCS trial procedure (ie, trial implant touches the skin). If data are missing for reasons other than an incomplete trial or therapy inefficacy, multiple imputations will be applied (based on all available lower limb pain VAS scores from baseline to 3 months). Responder rates will be compared using Fisher's exact test with a two-sided alpha level of 0.05, summarised across multiple imputations.

Box 2 Study endpoints*

Primary endpoint

The primary endpoint will include an assessment of changes in lower limb pain at 6 months. Participants will meet the primary endpoint if they are a pain responder, defined as having ≥50% reduction in lower limb pain score from baseline measured on a 10 cm Visual Analogue Scale (VAS). The proportion of pain responders will be compared between the treatment groups to evaluate the primary endpoint.

Secondary endpoints

The treatment groups will be compared for differences in the following outcomes:

⇒ Neurological improvement responder rate at 6 months.
  ⇒ A neurological improvement responder is defined as a participant who experiences an improvement in neuropathy from baseline, measured by a ≥3-point decrease on the modified Toronto Clinical Neuropathy Score (mTCNS) instrument (excluding changes in foot pain under symptom scores). Assessments will be performed by a trained clinician who is blinded to participants' study treatment.
⇒ Pain responder rate at 3 months.
⇒ Per cent change from baseline to 6 months in:
  ⇒ Lower limb pain (10 cm VAS).
  ⇒ Sleep (Pain and Sleep Questionnaire 3-item index).
⇒ Mean change from baseline to 6 months in:
  ⇒ Health-related quality of life (EuroQol 5-Dimensional 5-Level).
  ⇒ Neuropathy-related quality of life (Neuropathy-Specific Quality of Life Questionnaire).
  ⇒ Intraepidermal nerve fibre density at the lower calf.
  ⇒ Neurological function (mTCNS).
  ⇒ Haemoglobin A1c (HbA1c) for participants with type 2 diabetes and HbA1c≥8.0% at enrolment.
  ⇒ Body weight for participants with type 2 diabetes.

*Tertiary endpoints are presented in online supplemental table S3.

The first secondary endpoint will evaluate neurological improvement responder rates at 6 months, with neurological improvement response defined as a decrease of ≥3 points (excluding foot pain) in the total mTCNS from baseline. The 3-point threshold is based on the threshold for diabetes diagnosis in a recent validation study.[42] We will compare the proportion of neurological improvement responders between groups. Additional secondary and tertiary outcomes will be compared between and within treatment groups, as detailed in box 2 and online supplemental table S3. The primary analysis population for secondary endpoints will be per-protocol (PP): all randomised participants assigned to CMM alone who complete the 6-month primary assessment or those assigned to 10 kHz SCS+CMM who receive a permanent 10 kHz SCS system and complete the 6-month primary assessment. For secondary endpoint #2, a modified PP population at 3 months will be analysed: all randomised participants assigned to CMM alone who complete the 3-month assessment or those assigned to 10 kHz SCS+CMM who receive a permanent 10 kHz SCS system and complete the 3-month assessment.

If the primary endpoint reaches statistical significance at a two-sided alpha level of 0.05, secondary endpoints will be tested hierarchically in the order shown in box 2, with the same two-sided alpha level of 0.05 comparing the treatment groups until statistical significance cannot be demonstrated. Rates and proportions will be compared with Fisher's exact test, and continuous variables will be tested using Wilcoxon rank-sum tests.

The primary analysis population for tertiary endpoints will use the all-available-data population, summarised using descriptive statistics appropriate to the specific endpoints but not formally tested for statistical significance. Differences in outcomes will be compared between treatment groups up to 6 months and within treatment groups beyond 6 months. After the randomised comparison at 6 months, post-crossover analysis will be exploratory. Descriptive statistics will summarise all baseline and outcome data, with continuous variables summarised as means, SD, ranges and 95% CIs. Categorical variables will summarise frequency distributions. For all lower limb pain score analyses, a participant's right and left lower limb VAS scores will be averaged to generate a single score.

Poolability of sites will be tested using the PP population and will include all sites that enrol size or more subjects. Testing for a significant treatment effect between sites will be performed using a logistic regression model with a treatment-by-site interaction. If a difference in treatment effects is found across sites, a multivariate logistic regression analysis will be performed including all baseline characteristics that differ significantly across sites. Subgroup analyses for the primary and the first secondary effectiveness endpoints will examine sex, baseline lower limb pain severity (VAS<7.5 cm vs ≥7.5 cm), baseline mTCNS (<13 vs ≥13) and baseline HbA1c (<8.0% vs ≥8.0%). Subgroups will also be created to differentiate patients with increases, decreases or no significant change in medication, based on a blinded clinician's assessment and treatment effects will be compared between groups. We may conduct additional exploratory analyses to evaluate treatment effects for additional subgroups.

Exploratory analysis will also include examination of concordance between pain and neurological function responders, based on our prespecified responder threshold, using the kappa statistic. Spearman's correlation coefficients will be used to quantify relationships between continuous outcome variables such as percent pain reduction, mTCNS total score reduction, mTCNS sensory score reduction and IENFD increases. The sample size will likely be insufficient to assess predictors of discordant outcomes, but the observed patterns should inform future, larger studies to determine predictors of outcome.

Sample size

We calculated the sample size to adequately power both the primary and the first secondary endpoints. Based on the SENZA-PDN RCT results at 6 months, we used

lower limb pain responder rates of 85% in the 10 kHz SCS+CMM group and 5% in the CMM-alone group, with estimated neurological improvement responder rates of 40% and 10%, respectively.[43] Sample size calculations indicate that 47 participants per group are required to detect significant differences in the primary and first secondary endpoint with 90% power. Based on a potential 20% attrition rate and a 50% screening failure rate, the study will randomise 118 participants, targeting enrolment up to 236.

Interim analysis

A single interim analysis will occur when >50% of participants have completed the 6-month assessment, with three potential outcomes: (1) early trial termination for efficacy, (2) early trial termination for futility or (3) trial continuation with sample size reassessment. An independent third party will perform this analysis and provide a recommendation to the sponsor, with the sponsor and other study participants blinded from study results. The O'Brien-Fleming alpha spending function and Mehta and Pocock's promising zones for sample size re-estimation will be used for type I error control.

DISCUSSION

The FDA approved the Senza System (Nevro, Redwood City, California, USA) in July 2021 to manage chronic intractable lower limb pain associated with diabetic neuropathy. The recent SENZA-PDN study demonstrated long-term significant pain relief and quality of life improvements in participants treated with 10 kHz SCS. Notably, the study also revealed a potentially disease-modifying effect, with almost two-thirds (65.7%) of 10 kHz SCS recipients demonstrating a clinically meaningful improvement in neurological function at the 2-year mark, including improvements in sensory function, motor strength and reflexes in the lower limbs.[11] To our knowledge, such neurological improvement has not previously been reported for SCS or oral pharmacotherapies for PDN. This finding led to the FDA granting Breakthrough Device designation for the Senza System to address the potential of 10 kHz SCS to slow the progression of or improve sensory loss, motor weakness and reflexes in the lower limbs of patients with PDN.

Building on the promising results from the SENZA-PDN trial and other pilot studies, the PDN-Sensory RCT aims to collect Level 1 evidence to support this potential new indication by demonstrating the restoration of neurological function in a PDN population. To meet this goal, the study will use objective neurological endpoint measures, that is, the mTCNS and the IENFD biomarker.

The mTCNS was developed to capture early changes in the pathophysiology of DPN. The instrument has since been validated in a DPN population and correlated well with the severity of the disease.[27] The mTCNS uses a simple, quantitative scoring system that assesses both small and large fibre nerve function. The test's high inter-rater and intra-rater reliability[27] is particularly valuable for repeated assessments in a clinical trial setting and for identifying small changes in disease severity. Recent research by Idiaquez *et al* further validated the mTCNS by demonstrating its high diagnostic accuracy for polyneuropathy (98%). The authors recommended a cut-off value of ≥3 for diagnosing polyneuropathy, with 98.4% sensitivity and 85.7% specificity.[42]

Trained site personnel will collect minimally invasive skin biopsies for the IENFD analysis and quantification. This technique is widely regarded as the gold standard for diagnosing small fibre neuropathy, as recommended by the EFNS.[31 44 45] The IENFD measurement is objective and reproducible, with high inter-observer and intra-observer reliability—important factors in a multicentre, longitudinal clinical trial.[46] Laboratory analysis of IENFD will provide a precise measure of nerve fibre density, enabling evaluation of changes from baseline throughout the study. Standardised biopsy locations and central laboratory analysis will minimise the risk of variability. The IENFD laboratory assessments are performed blinded to treatment allocation.

The use of these objective neurological endpoints as criteria for treatment success is new to the SCS field and represents a key strength of the PDN-Sensory study. The IENFD biomarker outcome may also help develop our understanding of the mechanisms of action of 10 kHz SCS in relation to neurological changes in this PDN population.

Another strength of the study is the comprehensive set of patient-reported outcomes. The study will assess core outcome domains that are relevant to patients (eg, pain, physical and emotional functioning, global improvement, satisfaction with treatment and AEs, in line with the recommendations from the IMMPACT.[41] In addition, the study will evaluate HRQoL, sleep and metabolic parameters, providing a holistic evaluation of the effects of 10 kHz SCS. The study's pragmatic approach to participant selection (ie, those unresponsive to at least two PDN pain medications) is also in alignment with current SCS coverage criteria, which enhances the real-world relevance of the study.

However, the study has some limitations. First, the lack of an active control group, that is, LF-SCS, limits direct comparison between treatments. However, double-blinding would be impossible in 10 kHz SCS versus LF-SCS due to the necessity of paraesthesia during LF-SCS. While CMM better reflects the current standard of real-world care for PDN patients, comparing 10 kHz SCS with CMM also precludes the possibility of blinding study participants and clinical site personnel to treatment allocation because of the nature of device implantation—potentially biasing patient-reported and clinician-reported outcomes. However, we have mitigated this risk of bias in the key neurological endpoints by using blinded assessors for neurological evaluations and an objective biomarker measurement (IENFD). While we did not mandate or monitor adherence to specific

CMM treatment guidelines, the inclusion criteria specify a minimum prior pharmacotherapy regimen. Centre-specific CMM will continue as per the treating care team's standard practice and/or clinical treatment guidelines for PDN and diabetes. Another potential design limitation is the additional 6-month delay before permanent implantation for participants who cross over from CMM alone to receive permanent 10 kHz SCS. This delay may allow disease progression and impact clinical outcomes in the crossover cohort.

In summary, the PDN-Sensory RCT is the first SCS study to use objective neurological endpoints as criteria for success. It aims to provide Level 1 evidence supporting the use of 10 kHz SCS for pain relief and restoration of neurological function in patients with PDN. By incorporating the mTCNS and the IENFD biomarker, this study will provide the strongest evidence available of the effects of SCS in a PDN population. The results of this study could have significant implications for clinical practice and potentially expand the role of 10 kHz SCS in the management of this difficult-to-treat population.

DISSEMINATION

The study findings will be disseminated to relevant research, clinical, health service and patient communities through presentations at national and international conferences, and submitted for publication in a peer-reviewed journal with open access.

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Disclaimer The study sponsor designed the protocol in conjunction with a scientific advisory board. The site was not involved in data collection, and the interim analysis and the final statistical analysis will be performed by an independent statistician. Data monitoring and management will be performed by the sponsor. The sponsor, in collaboration with study investigators, will be responsible for the interpretation of the data, the writing of the report and the decision to submit the report for publication.

Competing interests RP-B has received research grants from NIDDK, Breakthrough T1D (formerly JDRF), Novo Nordisk Foundation, Bayer, Lexicon Pharma, Medtronic, Novo Nordisk; consulting fees from Averitas Pharma, Lexicon Pharma, Novo Nordisk, Nevro Corp., and Roche; has received support for attending meetings from Roche, participated on advisory board with Biogen, and is a member of the Board of Directors of the American Diabetes Association. ST has received grants for investigator-initiated studies or acted as a consultant, speaker for Angelini, AstraZeneca, Bayer, Berlin-Chemie, Confo-Therapeutics, Grunenthal, Medtronic, Merck, Merz, NeuroPN, Nevro, Novo Nordisk, P&G, Viatris, Withings, Worwag Pharma. EAP has received research support to her institution from Nevro, Saluda, SPR and Surgical Information Systems, and consulting fees from Abbott Neuromodulation, Biotronic, Medtronic Neuromodulation, Nalu, Nevro, Presidio Medical, Saluda, Verton, also honoraria and travel support from INS, NANS, Cleveland Clinic Pain Symposium and ASPN, participates in a leadership role for SynerFuse, ASPN, AANS/CNS Joint Section on Pain and owns stock or stock options from SynerFuse and Neuro.42. AB has received consulting fees from Nevro as a scientific advisor. DGA has received consulting fees from Nevro as a scientific advisor. GG has received payments as part of the speakers bureau for Eli Lilly, Abbott Diabetes, Sanofi and scientific advisory board for Nevro and MannKind. BL has received consulting fees as a scientific advisor, and honoraria for speaking and travel from Nevro Corp. DE has received consulting fees from Nevro in her capacity as an independent medical writer. MB, RA and DC are employees of Nevro Corp.

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