Neuromodulation: Technology at the Neural Interface

Received: January 30, 2025 Revised: March 10, 2025 Accepted: March 26, 2025

https://doi.org/10.1016/j.neurom.2025.03.074

Safety and Efficacy of Magnetic Peripheral Nerve Stimulation for Treating Painful Diabetic Neuropathy

Lora Brown, MD[1]; Emmanuel Gage, MD[2]; Harold Cordner, MD[3]; Leonardo Kapural, MD, PhD[4,5]; Jason Rosenberg, MD[6]; Marshall Bedder, MD[7,8]

ABSTRACT

Objectives: Current treatments for painful diabetic neuropathy (PDN) have variable effectiveness and known side effects. Noninvasive magnetic peripheral nerve stimulation (mPNS) provides effective pain relief without the side effects associated with interventional approaches. This study measured the differences in pain relief, sensory, and quality of life improvements using mPNS and conventional medical management (CMM) compared with sham and CMM in patients with PDN.

Materials and Methods: A multicenter, randomized clinical trial was conducted from December 2022 to November 2023. Patients were randomized to receive either mPNS and CMM or sham and CMM. Subjects were randomized to treatment groups in a 3:1 ratio to mPNS+CMM or Sham+CMM and observed for 30 days during the double-blinded phase (phase 1). At 30 days, the subjects in the Sham+CMM group could cross over to the mPNS group, initiating phase 2. All patients were followed up for 90 days after the first mPNS treatment. The primary end point was the between-group comparison of the proportion of responders, a subject who experienced ≥50% reduction from baseline in neuropathic pain measured by visual analog scale on day 30. Secondary end points included between-group comparison of percentage change from baseline for pain and numbness scores (days 30/90), responders to mPNS (day 90), and results from other quality-of-life measures (day 90).

Results: After 92 subjects were screened, 71 met the study inclusion/exclusion criteria and were treated. Subjects were similar in the groups, except for sex: 24 men (48%) in the mPNS group ($n = 50$) and 18 (85.7%) in the sham group ($n = 21$) ($p = 0.0096$). In the per-protocol analysis set, the mPNS group had a 72.3% responder rate (day 30) compared with 0% for sham (72.3% difference; 95% CI, 54.3–84.8; $p < 0.0001$), and 57.8% pain reduction from baseline, with 12.1% for sham. At day 90, mPNS had an 81.4% responder rate with 75.7% average pain reduction.

Conclusions: The data revealed that mPNS+CMM is superior to Sham+CMM at day 30 when used for treating pain from PDN. mPNS should be considered earlier in the treatment algorithm for PDN.

Clinical Trial Registration: The Clinicaltrials.gov registration number for the study is NCT05620225 (https://clinicaltrials.gov/study/NCT05620225). The study was first posted on November 9, 2022, and the first patient was enrolled on December 15, 2022.

Keywords: Magnetic peripheral nerve stimulation, noninvasive, pain relief, painful diabetic neuropathy, side-effect free

Address correspondence to: Marshall Bedder, MD, Department of Surgery, Pain Medicine Service, Charlie Norwood Veterans Administration Medical Center, 950 15th Street, Augusta, GA, 30904 4C-125, USA. Email: marshall.bedder@va.gov

[1] TruWell Health, St. Petersburg, FL, USA;
[2] Centurion Spine and Pain Centers, Brunswick, GA, USA;
[3] Florida Pain Management Associates, Vero Beach, FL, USA;
[4] Carolinas Pain Institute, Winston-Salem, NC, USA;
[5] Atrium Heath, Wake Forest Baptist Pain Center-Premier, Winston Salem, NC, USA;
[6] South Carolina Pain and Spine Specialists, Murrell's Inlet, SC, USA;
[7] Department of Surgery, Pain Medicine Service, Charlie Norwood Veterans Administration Medical Center, Augusta, GA, USA; and
[8] Department of Psychiatry and Health Behavior, Addiction Medicine Service, Wellstar/Medical College of Georgia, Augusta, GA, USA

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please see the journal's Guide for Authors.

Source(s) of financial support: This study was supported and funded by NeuraLace Medical, Inc.

INTRODUCTION

Painful diabetic neuropathy (PDN) is a debilitating condition characterized by chronic neuropathic pain resulting from damage to the myelin sheath of peripheral nerves and axonal loss, primarily affecting the lower extremities.[1] PDN may affect quality of life (QoL), contributing to psychologic distress and social dysfunction. Initial PDN treatment typically includes glycemic control and pharmacologic interventions, such as over-the-counter pain relievers (ibuprofen, aspirin), anticonvulsants (membrane stabilizers), and antidepressants (conventional medical management, CMM).[2] These treatments often provide incomplete relief, sometimes with significant side effects.[3] More invasive therapies, such as spinal cord stimulation (SCS), are used later in the treatment algorithm.[4] A systematic review reported 67% to 100% of patients experienced >50% pain relief 12 months after initiation of SCS therapy. However, SCS involves surgical implantation and risks such as lead migration, infection, pocket irritation, and explantation.[5] The increased risks and limited effectiveness of current therapies underscore the need for innovative, evidence-based PDN treatments.[2]

Magnetic peripheral nerve stimulation (mPNS) is Food and Drug Administration-approved for treating chronic and intractable posttraumatic and postsurgical pain and chronic PDN in the lower extremities. mPNS delivers biphasic, time-varying magnetic pulses that induce strong electrical fields in nerve bundles. These pulses are delivered at 0.2 to 5 Hz, typically 0.5 Hz.[6] Low-frequency pulses aim to induce action potentials and neuronal activity in the ascending and descending pathways of the peripheral and central nervous systems.[7]

mPNS treatment does not recruit smaller pain fibers, making it a more attractive option for patients with hypersensitivity. This lack of induced pain is due to the physics of the induced fields and the differential recruitment of nerve fibers within a bundle. mPNS recruitment is proportional to the inverse square of the fiber diameter.[8] A typical fiber diameter ratio of A-β (sensory) to A-Δ (pain) fibers is 3:1, yielding a recruitment ratio of 9:1. In contrast, other therapies, such as electrical PNS (ePNS) and transcutaneous electrical nerve stimulation, recruit A-β fibers in proportion to the inverse of the fiber diameter, at a 3:1 ratio.[9] This generates a higher proportion of undesirable A-Δ recruitment, reducing the beneficial A-β recruitment based on the patient's pain tolerance.

Each mPNS treatment lasted for approximately 13 minutes and at times induced slight motor contraction. Motor activity in the ascending and descending pathways of the PNS and CNS may increase plasticity changes in the brain as afferent neuronal signals are suppressed.[7] Competing treatments, such as percutaneous ePNS or implanted SCS, must function below the motor threshold to prevent discomfort. Moreover, neuromodulation with ultralow frequency waveforms (0.5–1 Hz) can reversibly block axonal conduction and chronic pain.[10]

In the recently published Safety and Efficacy of Axon Therapy (SEAT) study (which studied posttraumatic and postsurgical chronic neuropathic pain), mPNS showed superior efficacy to CMM. At three months, 71% of the subjects were deemed responders (>50% pain relief) in the mPNS+CMM group vs 13% of subjects in the CMM group.[11]

A pivotal multicenter, double-blind, randomized, sham-controlled clinical trial (RCT) was conducted to determine the pain relief, sensory, and QoL improvements derived from mPNS+CMM (the "mPNS Treatment") in the treatment of PDN, in comparison with Sham+CMM (the "Sham Treatment").

MATERIALS AND METHODS

Approvals and Informed Consent

This study adhered to the Declaration of Helsinki and good clinical practice guidelines. The protocol and informed consent forms were approved by the Western Institutional Review Board-Copernicus Group (WCG® IRB), Puyallup, WA, on November 8, 2022. The trial was registered at ClinicalTrials.gov with the unique identifier NCT05620225 (https://clinicaltrials.gov/study/NCT05620225). The study was first posted on November 9, 2022, and the first patient was enrolled on December 15, 2022.

Study Design and Population

The mPNS-PDN study was conducted in two phases. In phase 1, subjects were blinded and randomized 3:1 to mPNS Treatment or Sham Treatment and evaluated for 30 days. After unblinding in phase 2, participants in mPNS could continue treatment and be observed for another 60 days, whereas participants in Sham had the option to cross over to mPNS Treatment and be observed for 90 days to assess extended treatment effects. Consenting subjects were assessed for eligibility on the basis of the inclusion and exclusion criteria and randomized across six US sites. The key inclusion criteria were PDN for ≥six months (diagnosed by the subject's primary care or pain physician), being refractory to conservative treatment for ≥three months (including pain medications, physical therapy, and behavioral treatment), a pain intensity score of ≥5 of 10 on the visual analog scale (VAS), and no pain medications or a stable regimen (over-the-counter pain medications, prescription opioids, nonsteroidal antiinflammatory drugs, and anticonvulsants) for ≥28 days before enrollment. The key exclusion criteria included neuropathic pain due to postherpetic neuropathy, HIV, trigeminal neuralgia, carpal tunnel syndrome, central pain (eg, spinal cord injury), active psychologic or psychiatric disorders, and conditions affecting pain perception. Additional exclusion criteria included progressive neurologic diseases (eg, multiple sclerosis, brain or spinal cord tumors), body mass index >40, or A1C ≥9.0%. Although this A1C is too high for elective surgery such as SCS, and the high A1C group might be a very good target for this noninvasive alternative, the investigators concluded that an A1C of this magnitude might reflect a lack of glucose control and confound the study results.

Sample Size Calculation

The primary efficacy end point was a ≥50% reduction in diabetic neuropathy pain intensity at day 30, with no increase in baseline pain medication within four weeks before day 30. Pain intensity was measured using a ten-point VAS scale. Pilot data suggested 60% to 65% of responders in the mPNS+CMM group compared with 0% to 15% in the Sham+CMM group. Powering to the smallest difference (60%:15%) and assuming a 3:1 subject ratio in the mPNS+CMM to Sham+CMM group, with 90% power, 60 subjects (45:15) were needed to complete the study. Approximately 80 subjects were to be enrolled to account for ≥20% attrition.

Randomization and Blinding

Subjects diagnosed with PDN were randomized in a 3:1 ratio to either the mPNS+CMM or Sham+CMM group after final eligibility. An unbalanced group size was selected to expose more subjects to the therapy during phase 1 of the study and to minimize the risk to the study from excessive attrition in the Sham arm. Randomization

was generated using a permuted block size of four, stratified by site, to ensure within-site balance. It was assigned through the electronic data capture (EDC) system and was visible only to the "blinding operator," a designated clinical study team member (not the investigator or a therapy administrator) at each site. The blinding operator configured the EDC system to administer either mPNS or sham therapy on the basis of an automated blinding algorithm. All treatments were administered by the physician investigator (PI) or under the PI's supervision by another team member other than the blinding operator.

Both the participants and clinical staff (except the blinding operator) were blinded to the treatment. Device application appeared identical whether the subjects received sham or mPNS. Sham treatment was achieved by obscuring the coil and having the blinding operator reverse its orientation from active (toward the subject) to sham (away) on a per-subject basis. Blinding was maintained through strict permissions granted only to the blinding operator. At the day-30 visit, after the blinding effectiveness assessment, the subjects and treatment operator were unblinded. Participants were asked the following question: "What treatment

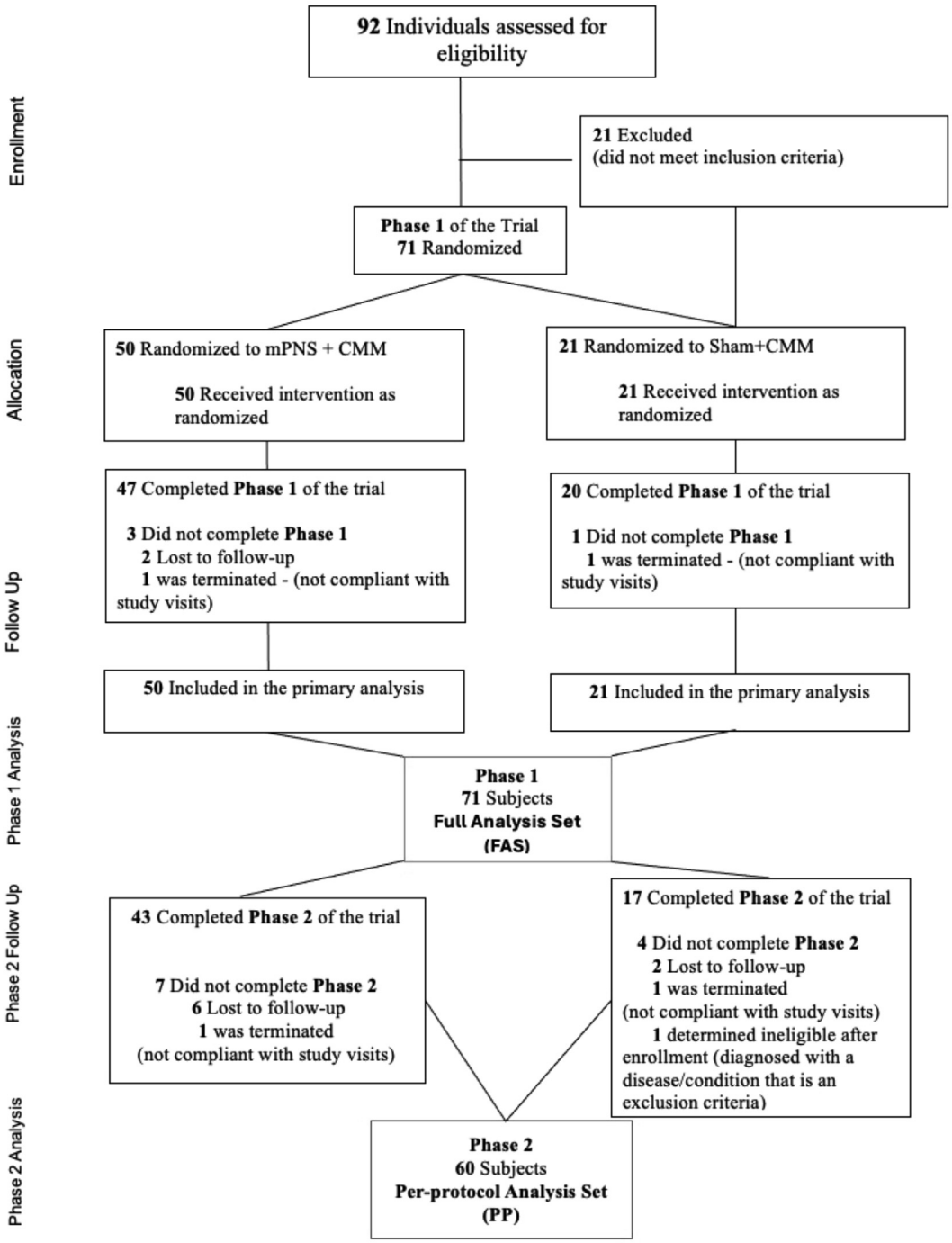

Figure 1. Consolidated Standards of Reporting Trials diagram.

group do you believe you were in?" They were then asked to choose one of the following three possible responses: Treatment, Sham, or not sure. If the 95% confidence interval (CIs) based on the James Blinding Index (BI) had an upper bound >0.5, blinding could be inferred.

Interventions

Per protocol, the participants first completed a seven-day self-assessment to measure pain scores, followed by a baseline clinical examination for those who met the inclusion criteria. Subjects scoring ≥5 on the VAS were randomized to receive mPNS or Sham Treatment. Analgesics were stabilized at a fixed dose 28 days before enrollment and monitored throughout the study, with adjustments allowed by the investigator, as needed.

At 30 days, the subjects in the Sham+CMM group could cross over to the mPNS group (the "Cross-Over mPNS"). The study continued to observe subjects from both the original mPNS and Cross-Over mPNS groups for 90 days.

Nerve Stimulation Procedure

The participants in the mPNS or Cross-Over mPNS groups received three treatments in the first week, followed by weekly treatments for the rest of the month. Biweekly treatments were administered for the next 60 days. Each mPNS procedure lasted 13.33 minutes per peripheral nerve (lower extremity nerves only), and PDN treatment was often bilateral, requiring two treatments per session. Investigators could adjust the intensity on the basis of the subject's needs and customize the treatment to target each subject's area of nerve damage.

During each treatment, subject information was entered in the mPNS system, including the pretreatment pain score and treatment location. A mapping procedure refined the exact treatment location and intensity, guided by the subject's feedback. Subsequently, 400 pulses were delivered while the locking arm held the coil in place. The operator could adjust the stimulus amplitude on the basis of feedback. The posttreatment pain score was then recorded.

Statistical Analysis

The full analysis set (FAS) adhered to the intent-to-treat principle, whereby all available data were included; subjects were analyzed according to their randomized group, irrespective of the treatment received. The per-protocol (PP) analysis set included all subjects who completed the day-30 visit (phase 1) without protocol deviations or missing visit data. For phase 2, the PP set included all subjects who completed the day-90 (or day 120 for Cross-Over mPNS) visit.

A fixed-sequence hierarchical testing strategy was applied to perform a confirmatory analysis of the primary and secondary efficacy end points in the FAS and PP populations. The primary end point was the proportion of responders, as measured by in-clinic VAS pain scores. Secondary end points included change in mean scores from baseline for VAS pain, European Quality of Life 5 Dimension 3 Level Scale (EQ-5D-3L), Patient Global Impression of Change, Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN), Pain Disability Index (PDI), Brief Pain Inventory (BPI), Depression Anxiety Stress Scales (DASS), VAS numbness, and any increase in baseline pain medication within four weeks of day 90 (day 120 for Cross-Over mPNS).

The primary end point at days 30 and 90 (day 120 for Cross-Over mPNS) was evaluated in the FAS and PP populations using a two-sided z-test of proportions. Effect sizes were calculated using Cohen's h for proportions, and two-sided exact 95% CIs were determined. Secondary end point testing followed a fixed-sequence approach, as specified. Statistically significant secondary end points underwent post hoc testing for subgroup differences (age, sex, and race) with Bonferroni correction. The primary efficacy outcome of VAS pain responder and two secondary outcomes (VAS pain and EQ-5D-3L change scores) were analyzed in sensitivity analyses and tested for treatment effect consistency using logistic regression or analysis of covariance models with a treatment-subgroup interaction term.

The incidence of adverse events (AEs) was summarized at days 30 and 90 (day 120 for Cross-Over mPNS) in the Safety Analysis Set/FAS. The χ^2 or Fisher exact test was used depending on the AE proportions. However, only one AE was reported (detailed in the safety results section); therefore, no statistical analysis was necessary.

Primary and secondary outcomes in subjects in the mPNS group across all three time points (0, 30, and 90 days) were modeled using mixed-effect models with repeated measures (MMRM), provided enough subjects remained in the study through phase 2. This exploratory analysis evaluated the potential differences in outcomes at 30 and 90 days. An α value of 0.05 was used. All analysis data sets and statistical outputs will be produced by the statisticians at EpidStrategies, Inc (Ann Arbor, MI), using the SAS system version 9.4 for Windows (SAS Institute Inc, Cary, NC).

RESULTS

The trial was conducted at six sites, with the first and last subjects enrolled in December 2022 and June 2023, respectively. The trial concluded when the final participant in Cross-Over mPNS

Table 1. Summary of Demographics, PP Population.

	CMM+mPNS (n = 43)	CMM+Sham (n = 17)	p Value
	n (%)	n (%)	
Age, mean (SD)	64.0 (9.0)	65.5 (7.8)	0.53
Sex			
Male	19 (44.2%)	14 (82.4%)	0.0096
Female	24 (55.8%)	3 (17.6%)	
Race			
White	35 (81.4%)	15 (88.2%)	0.71
Black or African American	8 (18.6%)	2 (11.8%)	
Not reported	0 (0%)	0 (0%)	

Table 2. Primary End Point in PP Population at Day 30.

	CMM+mPNS (n = 50) n (%)	CMM+Sham (n = 21) n (%)	Proportion difference (95.3% CI)	p Value
VAS pain responders	34 (72.3%)	0 (0.0%)	72.3% (54.3%, 84.8%)	<0.0001

An unpooled z-test for two proportions without continuity correction was used.

completed the 90-day visit in October 2023. Of the 92 subjects screened, 21 were excluded; 71 subjects were randomized, of whom 50 received mPNS+CMM and 21 received Sham+CMM. Through day 30, all subjects who completed the day-30 visit received six treatments (either mPNS or sham). Through day 90, all subjects receiving mPNS who completed the day-90 visit received ten treatments. From day 30 to day 120, all participants who crossed over group and completed the day-120 visit received ten mPNS treatments. All 71 subjects had PDN in the lower extremities. Of the 21 subjects in the Sham group, 20 chose to cross over on day 30; 60 subjects completed the study by day 90. Eight subjects (six mPNS, two Sham) were lost to follow-up, and three (one mPNS, two Sham) had their participation terminated before completion (Fig. 1). No protocol deviations were observed.

The demographics (Table 1**)** were generally similar in the two treatment groups. However, in the Sham+CMM group, there was an uneven majority of men in the PP group (82.4% male). Results from sensitivity subgroup analyses (data not shown) showed no statistically significant differences in treatment effects based on sex for the VAS responder rates, VAS change score, or EQ-5D-3L change score (p = 0.85, p = 0.64, and p = 0.25, respectively). Baseline characteristics, physical examination, medical history, and surgical history also were similar in the groups (data not shown).

Primary Outcomes End Point Evaluation

The primary end point was defined as ≥50% reduction in the VAS pain score on day 30 without an increase in pain medication within the previous four weeks. No subjects in the mPNS or Sham group reported increased pain medication use at days 30 or 90. In the PP populations, 34 of 50 participants (72.3%) with mPNS were responders, with 0 responders (0%) in the Sham group (day 30), yielding a 72.3% responder difference (95% CI, 54.3–84.8; p < 0.0001) (Table 2). This result should not be taken to indicate that there was no sham response; the later results present the mean VAS score for Sham.

Secondary End Point Evaluations

At day 30, for the mPNS treatment group, the mean change in VAS pain score (in clinic) from baseline was −4.04 (SD = 2.45; 95% CI, −4.76, −3.32) for the PP population. For the Sham group, the mean VAS score change was −0.81 (SD = 1.76; 95% CI, −1.63, 0.02), indicating that a placebo effect was observed in the study. The difference in the mean change from baseline between the two groups was −3.23 (p < 0.0001) (Table 3). The percentage reduction in VAS pain scores showed a −57.6% reduction for mPNS vs −12.5% for Sham (for a difference of −45.1%). In the FAS and PP populations, 35 subjects with mPNS (70.0% and 81.4%, respectively) and 15 subjects in the mPNS Cross-Over group (75% and 88.2%, respectively) were responders at day 90 (data not shown).

The mean VAS pain scores in the PP population are presented in Figure 2. At day 90, the change from baseline in the mPNS group was −5.28 (SD = 2.37; 95% CI, −6.01, −4.55). In the PP population, the mean change from baseline VAS pain score (day 30) was −4.11 (SD = 2.28; 95% CI, −4.81, −3.41) in the mPNS group and −0.82 (SD = 1.78; 95% CI, −1.74, 0.09) in the Sham group, a difference of −3.29 (95.3% CI, −4.54. −2.03; p < 0.0001) (Fig. 2).

MMRM for VAS pain score (day 30), which was adjusted for baseline VAS pain score and opioid use at baseline, revealed significant differences between mPNS and Sham in both FAS and PP (p < 0.0001 FAS and PP): FAS mPNS (−3.95; SD = 0.29; 95% CI, −4.54, −3.36) versus FAS Sham (−1.01; SD = 0.45; 95% CI, −1.92, −0.11) and PP mPNS (−4.04; SD = 0.29; 95% CI, −4.61, −3.47) versus PP Sham (−1.00; SD = 0.46; 95% CI, −1.92, −0.09). MMRM for VAS pain score through day 90 in mPNS also was significant in both FAS (−5.24; SD = 0.34; 95% CI, −5.93, −4.56; p = 0.0006) and PP (−5.28; SD = 0.32; −5.93, −4.63; p = 0.0007), suggesting continued improvement through 90 days.

Table 3. Secondary End Points in PP Population at Day 30.

	CMM+mPNS (n = 47) n Mean change from baseline (SD)	CMM+Sham (n = 20) n Mean change from baseline (SD)	Difference*	p Value
Change in VAS pain scores (in clinic)	47 −4.04 (2.45)	20 −0.81 (1.76)	−3.23 (−4.46, −2.01)	<0.0001
Change in VAS numbness	47 −2.29 (3.01)	20 −0.13 (2.44)	−2.16 (−3.68, −0.64)	0.0061
Change in EQ-5D-3L	47 0.08 (0.19)	20 0.01 (0.15)	0.07 (−0.03, 0.17)	0.16
Change in QOL-DN (total)	45 −8.36 (15.57)	19 −0.05 (13.62)	−8.30 (−16.5, −0.08)	0.048
PGIC Status (n (%))				
Improved	38 (80.9%)	7 (35.0%)	45.9% (19.1%, 67.5%)	0.0005
Nonimproved	9 (19.1%)	13 (65.0%)		

Improved, much better and slightly better; nonimproved, no change, slightly worse, and much worse.
PGIC, Patient Global Impression of Change.
*95% or 95.3% CIs.

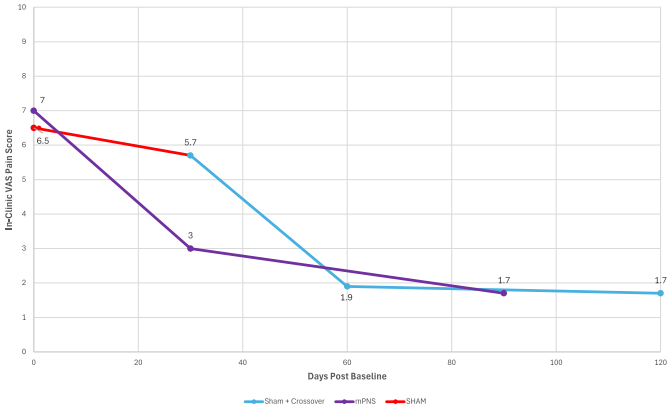

Figure 2. Mean VAS pain scores—mPNS vs Sham+Crossover, PP population.

At day 90, in both the FAS and PP, the EQ-5D-3L score change from baseline in the mPNS group was 0.14 (SD = 0.21). MMRM of the EQ-5D-3L score through day 90 in mPNS was significant in both FAS (0.15; SD = 0.03; 95% CI, 0.09–0.20; $p = 0.019$) and PP (0.14; SD = 0.03; 95% CI, 0.09–0.20; $p = 0.023$), indicating continued improvement throughout the study.

In the PP population, the mean change from baseline in the VAS numbness score at day 30 was −2.46 (SD = 3.00; 95% CI, −3.39, −1.54) in the mPNS group and −0.17 (SD = 2.53; 95% CI, −1.47, 1.13) in the Sham group, a difference of −2.29 (95% CI, −3.94, −0.64; $p = 0.0073$). At day 90, the change from baseline in the PP mPNS group was −3.54 (SD = 3.29; 95% CI, −4.55, −2.52), identical to the FAS, a 52% reduction (Fig. 3). After adjusting for baseline score and opioid use at baseline, MMRM from day 30 through day 90 in the mPNS group was significant in both FAS (−3.43; SD = 0.40; 95% CI, −4.25, −2.62; $p = 0.0024$) and PP (−3.54; SD = 0.42; 95% CI, −4.38, −2.70; $p = 0.0033$), suggesting continued improvement through 90 days.

After 90 days of treatment, the mPNS+CMM group showed improvements in other key secondary outcomes (Table 4). Subjects in the Cross-Over mPNS group also showed significant improvements in numbness, QOL-DN, PDI, and BPI scores after 90 days, whereas DASS scores remained stable across the depression, anxiety, and stress dimensions. The blinding effectiveness assessment showed that it was effective, and blinding could be inferred, with the James BI having an upper CI of 0.520 (Table 5).

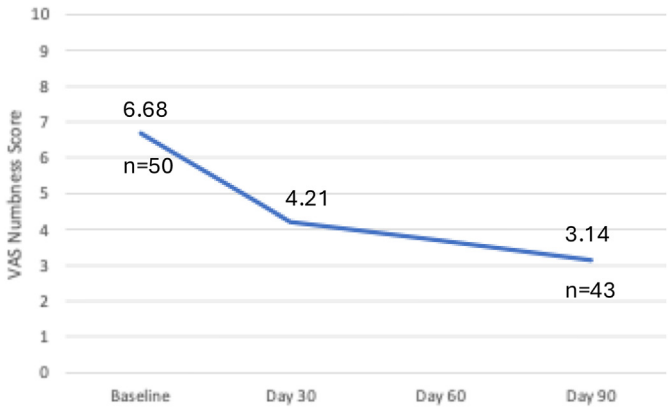

Figure 3. Mean VAS numbness scores, PP population.

Table 4. Change in Sensory and QoL Measures From Baseline to Day 90, PP Population.

	mPNS+CMM	Crossover to mPNS+CMM
	Mean change (95% CI)*	Mean change (95% CI)*
VAS numbness (in-clinic)	−3.54 (−4.55, −2.52)	−2.42 (−3.95, −0.90)
QOL-DN	−12.07 (−18.47, −5.67)	−15.53 (−25.40, −5.66)
PDI	−11.17 (−17.41, −4.93)	−15.59 (−21.46, −9.71)
BPI	−2.52 (−3.29, −1.75)	−1.84 (−2.78, −0.90)
DASS—depression	−2.33 (−4.48, −0.17)	−2.24 (−5.57, 1.09)
DASS—anxiety	−2.47 (−4.48, −0.45)	−2.29 (−4.84, 0.25)
DASS—stress	−4.65 (−7.78, −1.52)	−1.88 (−4.72, 0.96)

*Negative change score values indicate improvement in all sensory and QoL measures.

Safety

No treatment- or device-related AEs or AEs leading to withdrawal or death were reported in either group. One participant (2%) in the mPNS group with an extensive history of cardiovascular morbidity reported the only AE, a serious AE that occurred three months after enrollment and was unrelated to the device or treatment. The patient was hospitalized for myocardial infarction, leading to quadruple coronary artery bypass graft surgery. Before this event, the subject had been a responder with a baseline in-clinic VAS pain score of 7.5 and day 30 in-clinic VAS pain score of 1.1. The VAS pain score after the patient's last recorded mPNS treatment was 0.0.

DISCUSSION

To our knowledge, this mPNS-PDN study is the first prospective, multicenter RCT to indicate the superiority of mPNS+CMM to Sham+CMM. Although there was a measurable Sham response of a mean VAS score change of −0.81 (for Sham+CMM), the mean VAS score change of −4.04 for mPNS+CMM was a statistically significant difference. The high pain responder rate at 90 days (FAS 70.0%; PP 81.4%) and pain reduction (FAS 75.7%; PP 75.5%) were statistically significant. These findings are similar to those of the recently published SEAT study.[11] The SEAT study was the first multicenter RCT to show the superiority of mPNS+CMM to CMM alone. In the PP analysis, 22 subjects (71.0%) in the mPNS+CMM group and three subjects (13.0%) in the CMM group were responders (>50% pain relief; $p < 0.0001$). At day 90, the mean change in VAS pain score was −3.76 (SD: 2.16) in mPNS+CMM compared with −0.70 (SD: 2.16) in CMM; $p < 0.0001$.

These results rival the effectiveness of invasive procedures such as temporary or implanted peripheral nerve stimulators and spinal cord stimulators[2,4,5,12] but without their periprocedural pain or surgical risks.[9] No participants in the mPNS group in the study

Table 5. Blinding Effectiveness at Day 30, PP Population.

James BI*	Estimate	SE	95% CI
	0.40	0.0623	(0.27, 0.52)

*Computed using the BI package in R.

increased their pain medication usage, indicating a potential benefit in avoiding the side effects of higher CMM dosages and opioid dependency.[3] The mPNS-PDN study results mirror those from the Bedder mPNS retrospective analysis.[13]

The mPNS-PDN study yielded statistically significant relief of pain and numbness, and improvements in QoL, warranting further investigation in larger populations. These results, achieved without side effects, suggest that mPNS could play a greater role in earlier PDN intervention. Additional neuropathic pain conditions, such as chemotherapy-induced peripheral neuropathy, should be explored.

Limitations

A review of QOL-DN data collection revealed that questions related to the QOL-DN symptoms domain intended for multiple body areas were only collected for one area. Consequently, the total QOL-DN and symptoms domain scores cannot be interpreted within the context of the validated QOL-DN questionnaire and published scores from other trials. Therefore, the QOL-DN results should be interpreted with this limitation in mind. Another consideration is the interaction between pain medication and mPNS. Investigators could adjust the subjects' pain medications during the study. Although no increases were observed in the mPNS group, changes in opioid analgesics could potentially confound the effects of mPNS. Because the study was not designed to address medication or psychologic issues related to chronic pain medication use, the impact of mPNS on chronic opioid use warrants further investigation. Finally, the study duration of 90 days limited the time the participants were observed. In a longer study of mPNS and PDN, once-per-month maintenance treatments would be required to maintain durable pain relief.

CONCLUSIONS

The mPNS-PDN study results at 30 and 90 days are both statistically and clinically significant. Pain relief, sensation, and QoL improvements were shown with high confidence. Pain responder rates ranged from 70.0% to 81.4%, a level previously only achieved by invasive treatments. As a noninvasive procedure, mPNS offers the benefits of neuromodulation with a significantly lower risk. This new evidence reinforces the value of mPNS, supported by the recently published Systematic Guideline by the ASPN Workgroup on the Evidence,Education, and Treatment Algorithm for Painful Diabetic Neuropathy (SWEET) guideline,[2] which suggest that mPNS should be considered early in the chronic PDN treatment algorithm, directly after CMM and before any invasive procedures.

Acknowledgements

The authors thank Joe Milkovits, President of NeuraLace Medical, for technical support in the production of this manuscript; JoAnn Kuhne, Kara & Associates, for clinical trial management; Heidi Reichert, ToxStrategies, for support with the statistical analysis; Danielle Cox and Carlos Zavala for management of trial operations; and Alanna Cordner for manuscript support.

Data Availability

The Principal Investigator takes responsibility for the integrity of the data and the accuracy of the data analysis, and once unblinded, had full access to all the data in the study. The data supporting the findings of this study are available from the Principal Investigator on request.

Authorship Statements

Lora Brown, Emmanuel Gage, Harold Cordner, Leonardo Kapural, and Jason Rosenberg designed and conducted the study, including patient recruitment, data collection, and data analysis. Leonardo Kapural and Marshall Bedder designed the study and prepared the manuscript draft with important intellectual input from Lora Brown and Harold Cordner. Leonardo Kapural and Marshall Bedder provided input in analyzing the data. Lora Brown, Emmanuel Gage, Harold Cordner, Leonardo Kapural, Jason Rosenberg, and Marshall Bedder had complete access to the study data. All the authors approved the final manuscript.

Conflict of Interest

Marshall Bedder is a paid consultant for NeuraLace Medical, Inc and a consultant for Boston Scientific; and chairs the Advisory Board for Neuralace Medical. Jason Rosenberg is a consultant for Neuralace Medical. Leonardo Kapural serves on the advisory boards of Biotronik, Gimer, Neuralace, PainTEQ, and Presidio and has research agreements with Neuros, Nevro, FUS Mobile, Saluda, and Nalu. The remaining authors reported no conflict of interest.

How to Cite This Article

Brown L., Gage E., Cordner H., Kapural L., Rosenberg J., Bedder M. 2025. Safety and Efficacy of Magnetic Peripheral Nerve Stimulation for Treating Painful Diabetic Neuropathy.
Neuromodulation 2025; ■: 1–8.

REFERENCES

1. Schreiber AK, Nones CF, Reis RC, Chichorro JG, Cunha JM. Diabetic neuropathic pain: physiopathology and treatment. *World J Diabetes*. 2015;6:432–444. https://doi.org/10.4239/wjd.v6.i3.432.
2. Sayed D, Deer TR, Hagedorn JM, et al. A systematic guideline by the ASPN workgroup on the evidence, education, and treatment algorithm for painful diabetic neuropathy: SWEET. *J Pain Res*. 2024;17:1461–1501. https://doi.org/10.2147/JPR.S451006.
3. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14:162–173. https://doi.org/10.1016/S1474-4422(14)70251-0.
4. Petersen EA, Stauss TG, Scowcroft JA, et al. Long-term efficacy of high-frequency (10 kHz) spinal cord stimulation for the treatment of painful diabetic neuropathy: 24-month results of a randomized controlled trial. *Diabetes Res Clin Pract*. 2023;203, 110865. https://doi.org/10.1016/j.diabres.2023.110865.
5. Henson JV, Varhabhatla NC, Bebic Z, et al. Spinal cord stimulation for painful diabetic peripheral neuropathy: a systematic review. *Pain Ther*. 2021;10:895–908. https://doi.org/10.1007/s40122-021-00282-9.

6. Leung A, Fallah A, Shukla S. Transcutaneous magnetic stimulation (TMS) in alleviating post-traumatic peripheral neuropathic pain states: a case series. *Pain Med*. 2014;15:1196–1199. https://doi.org/10.1111/pme.12426.
7. Deer TR, Eldabe S, Falowski SM, et al. Peripherally induced reconditioning of the central nervous system: a proposed mechanistic theory for sustained relief of chronic pain with percutaneous peripheral nerve stimulation. *J Pain Res*. 2021;14:721–736. https://doi.org/10.2147/JPR.S297091.
8. Basser PJ, Roth BJ. Stimulation of a myelinated nerve axon by electromagnetic induction. *Med Biol Eng Comput*. 1991;29:261–268. https://doi.org/10.1007/BF02446708.
9. McNeal DR. Analysis of a model for excitation of myelinated nerve. *IEEE Trans Biomed Eng*. 1976;23:329–337. https://doi.org/10.1109/tbme.1976.324593.
10. Jones MG, Rogers ER, Harris JP, et al. Neuromodulation using ultra low frequency current waveform reversibly blocks axonal conduction and chronic pain. *Sci Transl Med*. 2021;13:eabg9890. https://doi.org/10.1126/scitranslmed.abg9890.
11. Kapural L, Patel J, Rosenberg JC, Li S, Amirdelfan K, Bedder M. Safety and efficacy of axon therapy (SEAT study), utilizing magnetic peripheral nerve stimulation (mPNS) for treatment of neuropathic pain. *J Pain Res*. 2024;17:3167–3174. https://doi.org/10.2147/JPR.S481944.
12. Petersen EA, Stauss TG, Scowcroft JA, et al. Effect of high-frequency (10-kHz) spinal cord stimulation in patients with painful diabetic neuropathy: a randomized clinical trial. *JAMA Neurol*. 2021;78:687–698. https://doi.org/10.1001/jamaneurol.2021.0538.
13. Bedder M, Parker L. Magnetic peripheral nerve stimulation (mPNS) for chronic pain. *J Pain Res*. 2023;16:2365–2373. https://doi.org/10.2147/JPR.S409331.