

# Efficacy and Safety of Magnetic Peripheral Nerve Stimulation for Treatment of Neuropathic Pain; One Year Follow Up of Long-Term Outcomes

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**Objective:** Magnetic Peripheral Nerve Stimulation (mPNS) is an emerging neuromodulation therapy for chronic pain. We aimed to assess the safety and efficacy of mPNS in combination with CMM in patients with post-traumatic or post-surgical pain.

**Materials and methods:** Safety and Efficacy of Axon Therapy (SEAT) was a prospective, randomized, multi-center study conducted across four clinical sites in the United States with 1 year follow-up. Eligible participants were between 18–75 years old, had chronic neuropathic pain for at least three months, and a baseline visual analog scale (VAS) score of 6 or higher. Subjects were randomized 1:1 to receive either Magnetic Peripheral Nerve Stimulation (mPNS) along with their Conventional Medical Management (mPNS+CMM) or CMM alone. Subjects in CMM cohort were allowed to crossover at Day 90. The primary efficacy endpoint was the number of subjects with  $\geq 50\%$  reduction of pain intensity at Day 90 without an increase in pain medication. The primary safety endpoint was the proportion of subjects free from therapy-related adverse events at Day 90. This trial is registered with ClinicalTrials.gov, NCT04795635.

**Results:** 90 participants were screened, and 65 met the inclusion criteria to be enrolled (CMM + mPNS 35; CMM: 30). At Day 90, 71% of subjects were considered responders ( $>50\%$  pain relief) in the CMM + mPNS cohort vs 13% of subjects in the CMM group ( $p < 0.0001$ ). By the end of the study, 94% of participants were determined to be pain responders in the CMM + mPNS group as well as 69.2% in the Crossover group. The EQ-5D-3L and PGIC responder rates also improved. AEs were considered to be treatment-related in three (8.6%) CMM + mPNS participants, and two (10.5%) Crossover participants.

**Conclusion:** mPNS was well-tolerated and resulted in significant long-term reductions in pain intensity and improvement in patients with chronic neuropathic pain.

**Keywords:** magnetic peripheral nerve stimulation, noninvasive, pain relief, side-effect free

## Introduction

Chronic neuropathic pain remains a significant clinical challenge, profoundly affecting patients' quality of life by contributing to emotional distress and social limitations.<sup>1</sup> Despite the variety of available treatments, their effectiveness is often insufficient for individuals with severe and persistent pain. Improvements in the quality of the development and presentation of clinical practice guidelines are needed, in addition to more efficacy evidence for the management of patients with neuropathic pain.<sup>2</sup> Common pharmacological approaches, including, antidepressants, membrane stabilizers, and opioid analgesics, demonstrate limited success, with high number of patients needed to treat to achieve meaningful pain relief.<sup>3</sup> More invasive strategies, such as nerve denervation or implantation of neuromodulation devices like subcutaneous peripheral nerve stimulation, lack sufficient long-term efficacy data.<sup>4</sup>



Magnetic Peripheral Nerve Stimulation (mPNS) has received FDA clearance for managing chronic and intractable post-traumatic, post-surgical neuropathic pain and painful diabetic neuropathy (PDN) of the lower extremities. Results from a recent multi-center RCT demonstrated superiority of using mPNS together with conventional medical management (CMM) over Sham+CMM for treating PDN.<sup>5</sup> This technique utilizes biphasic, time-varying magnetic pulses to generate strong electrical fields in targeted nerve bundles, aiming to activate both peripheral and central nervous system pathways. With a typical frequency range of 0.2 to 5 Hz, commonly applied at 0.5 Hz, mPNS is designed to elicit neuronal responses without causing significant discomfort.<sup>6,7</sup> The differential recruitment of nerve fibers—favoring A-beta sensory fibers over A-delta pain fibers—contributes to its tolerability, in contrast to conventional electrical PNS or transcutaneous electrical nerve stimulation (TENS), which may lead to increased pain sensitivity.<sup>8</sup>

mPNS is administered in structured sessions, beginning with three applications in the first week, followed by a decreasing frequency over the trial period. This approach allows for the reducing pain signaling through both ascending and descending neural pathways.<sup>7</sup> Alternative neuromodulation strategies, such as percutaneous electrical PNS or spinal cord stimulation (SCS), necessitate operation below the motor threshold to avoid patient discomfort, whereas mPNS offers a non-invasive, well-tolerated alternative.<sup>9</sup>

Given the need for rigorous clinical evaluation, this clinical trial (the SEAT study) aimed to compare the safety and efficacy of mPNS combined with CMM to CMM alone in patients with chronic peripheral neuropathic pain. This manuscript provides a longer follow up (12 months) compared to the original publication of the 90 day data.

## Methods

### Study Design and Participants

A randomized trial was conducted in the United States at four clinical sites (Center for Clinical Research, Winston Salem, NC; IPM Medical Group, Walnut Creek, CA; Crescent Moon Research, Murrell's Inlet, SC; National Spine and Pain, Shrewsbury, NJ). Eligible patients had to have chronic neuropathic pain for  $\geq 3$  months and a baseline VAS score  $\geq 6$ . Full eligibility and exclusionary criteria can be seen in [Table 1](#). The most common entries in Surgical History were Arthroplasty, Arthroscopy, Cholecystectomy and Hysterectomy. The anatomical locations treated were all peripheral nerves, with ~60% being on the lower limbs. Participants were recruited from an existing patient population within the clinics and through social media marketing. All patients provided written consent before any assessments were conducted, including screening.

The trial adhered to the regulatory requirements set forth by the US Code of Federal Regulations and aligned with ethical principles outlined in the Declaration of Helsinki by the 18th World Medical Assembly. Approval for the study protocol and informed consent documentation was granted by the Central Institutional Review Board (Western

**Table 1** Summary of Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Men or women of any race or ethnicity who are 18–75 years of age.	Currently diagnosed with a progressive neurological disease.
Chronic peripheral neuropathic pain present for more than three months after a traumatic or surgical event, per medical history.	Other pain that may confound assessment or self- evaluation of the peripheral neuropathic pain
A score $\geq 6$ on VAS at Enrollment / Screening Visit	A diagnosis of malignancy other than basal cell carcinoma or carcinoma in situ of the cervix, within the past five years, to include life expectancy less than 1 year due to advanced malignancy.
Implicated peripheral nerve(s) have been identified and documented in their medical record.	Implantable “electrical” medical devices within four inches or less of the site of pain to be treated by mPNS.
	Other factors (such as severe health conditions or laboratory abnormalities) that may interfere with study compliance or the interpretation of study results and would make the subject inappropriate to participate in the study.

Institutional Review Board (WIRB)-Copernicus Group (WCG<sup>®</sup> IRB), Puyallup, Washington). The IRB approval reference number is 20211102. This trial is registered with ClinicalTrials.gov, NCT04795635.

Following determination of final study eligibility at the conclusion of the Baseline visit, subjects were randomly assigned in a 1:1 fashion to receive either mPNS along with their Conventional Medical Management (CMM+mPNS) or CMM alone as previously described.<sup>10</sup> Randomization was generated utilizing a permuted block size of four, stratified by study site to ensure within-site balance. Randomization was assigned using the randomization module in the electronic data capture (EDC) system by the appropriate clinical study team member at the clinical site. Subjects were not considered enrolled in the study until they received randomization assignment. Screen failures were tracked and the reasons for screen failures were recorded. Investigators and study subjects were not blinded to the assigned treatment group, due to the nature of the intervention, however those analyzing the data were masked to group assignment.

## Procedures

Treatment was administered using the mPNS device as previously described.<sup>10</sup> Briefly, after proper positioning, the device operated at a stimulation frequency of 0.5 Hz per pulse, covering an intensity range from 1% to 100% of the magnetic stimulator's output. The waveform of each stimulation pulse was a single harmonic cycle lasting approximately 280–290 microseconds. Each session, which lasted 13.33 minutes, delivered around 400 pulses to the patient.<sup>10</sup>

The mPNS+CMM protocol began with three consecutive daily sessions in the first week for participants in mPNS treatment arm. Following this, participants received a weekly session for the remainder of the month, totaling six treatments. Over the subsequent 60 days, treatments were administered twice per month, transitioning to monthly sessions as needed for the remainder of the study. Assessments were conducted at baseline, Day 30, Day 90, Day 120, and on Day 365.

The primary efficacy endpoint at Day 90 was the percentage of “pain responders” who experience 50% or greater reduction in neuropathic pain intensity as measured by in-clinic visual analog scale (VAS) for the primary area of pain, with no increase in baseline pain medications. Exploratory endpoints analyzed included pain responders at Day 365, average changes in pain scores from baseline, reduction in morphine-equivalent daily dose (MEDD), initiation of new pain medication, and increases in new pain medication.

Secondary endpoints included Day 365 patient-reported outcomes: European Quality of Life 5 Dimensions 3 Level (EQ-5D-3L) scores, Patient Global Impression of Change (PGIC) scores and Pain Disability Index (PDI) scores.

The primary safety endpoint was defined as a between groups comparison of the proportion of subjects free from treatment-related adverse events (TRAE) by end of study.

## Analysis of Data for the Crossover Arm

Since participants in the CMM alone arm were allowed to crossover to CMM + mPNS on Day 90, the baseline data presented for the Crossover group occurred at study Day 90, the data presented for Day 90 occurred at study Day 180, and the data presented for Day 365 occurred at study Day 450.

## Statistical Analysis

For continuous variables, descriptive statistics were summarized using means and standard deviations to represent central tendencies, while dichotomous data were expressed as percentages. Changes in pre-pain scores over time were analyzed using a mixed-effects model for repeated measures.

Mixed-effect models with repeated measures (MMRM) were used to evaluate the primary, secondary and exploratory endpoints. The response variable is the change from Baseline to EOS. The model included the following fixed effects:

- Treatment Group
- Visit
- Baseline level of VAS pain, as continuous covariate
- Treatment-by-visit interaction
- Concomitant opioid use at baseline

Sample size calculations were based on the expectation that at least 50% of participants in the CMM+mPNS group will respond to treatment, while the response rate in the CMM group may be around 10%. The projected responder rate for the test group (>50%) was based on findings from a prior pilot study. To achieve a minimum of 95% power in demonstrating the superiority of CMM+mPNS over CMM at a one-sided significance level of 0.05, at least 28 participants per group were needed. To account for potential dropouts after randomization, the total planned enrollment was approximately 60 participants, with around 30 in each group.

The primary analysis for this trial was conducted once the final participant completed their day 90 visit. Data was generated and analyzed for the per protocol (PP) population. To assess the primary and secondary efficacy endpoints, a hierarchical fixed-sequence testing strategy was applied, using an alpha level of 0.05 for between-group comparisons of CMM + mPNS versus CMM alone. The endpoints were analyzed in the following order: pain responders; mean VAS scores, EQ-5D-3L scores, and PGIC scores.

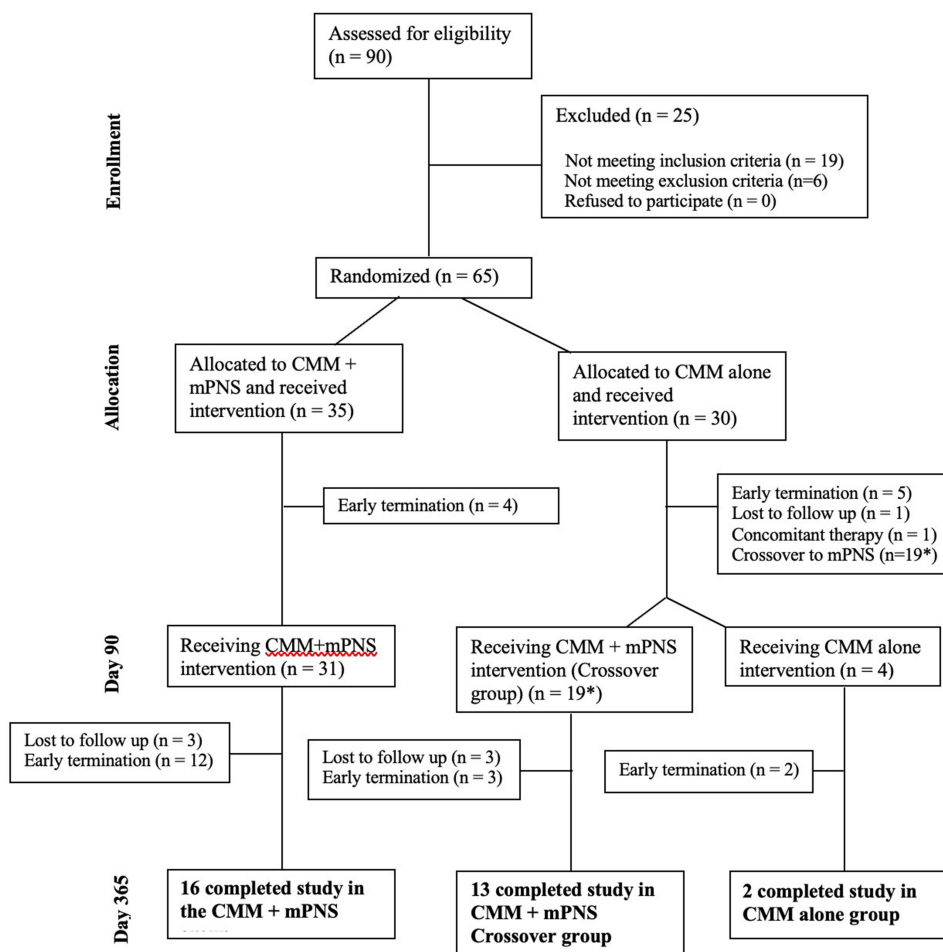
Since the primary endpoint reached statistical significance in a one-sided test at  $\alpha = 0.05$ , the analysis proceeded to evaluate secondary endpoints. These were tested sequentially in the pre-specified order using two-sided tests at an alpha level of 0.05. Any secondary endpoint that met statistical significance underwent additional post-hoc subgroup analyses (eg, by age, race, or gender), applying a Bonferroni correction. If statistical significance was not achieved for a given endpoint, hierarchical testing was discontinued, and any further analyses of secondary endpoints were considered exploratory. Additionally, adverse events reported through day 90 were assessed and compared between groups within the safety analysis set. All analysis data sets, and statistical outputs were produced by the statisticians at EpidStrategies, Inc., using the SAS system version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Sensitivity analyses utilizing the last observation carried forward (LOCF) method were performed, and the findings remained consistent with the primary endpoint analysis.

## Results

Between May 2021 and March 2023, 90 participants were recruited and screened for eligibility, with the majority of study enrollments screened at Sites 1 and 3 (Figure 1). Of the screened participants, 25 did not meet the eligibility criteria, resulting in a total of 65 enrolled participants, with 35 participants assigned to the CMM + mPNS group, and 30 assigned to CMM alone. All enrolled participants met the study's inclusion and exclusion criteria, with the most common reason for screen failure being a VAS score below 6 at screening/enrollment. By Day 90, nine participants (four in CMM + mPNS and five in CMM) withdrew from the study before completion. Additionally, within the CMM group, one participant was lost to follow-up, and one participant violated protocol by using a prohibited concomitant therapy. Therefore, the Safety Analysis Set (SAF) included 65 participants, while the Per Protocol (PP) set comprised of 54 participants with 31 participants in the CMM + mPNS group, and 23 participants in CMM alone. On Day 90, participants in the CMM alone group were allowed to voluntarily crossover to CMM + mPNS treatment for the rest of the study. 18 participants chose to transition from CMM to CMM + mPNS, leaving five participants remaining in the CMM alone group, 18 in the Crossover group, and 31 participants in the CMM + mPNS by Day 90. One more additional participant crossed over after Day 90 but before Day 120 for a total of 19 participants in the Crossover group. By Day 365, 18 additional participants terminated early (12 from CMM + mPNS, three from CMM, and three from the Crossover group), and six participants were lost to follow-up (three from CMM + mPNS, three from Crossover). By the end of the study, 16 participants remained in the CMM + mPNS group, 2 remained in the CMM alone group, and 13 remained in the Crossover group.

Baseline demographic characteristics were comparable between the CMM + mPNS and CMM groups (Table 2). The median age was slightly lower in the CMM + mPNS group (60.0 years) compared to the CMM alone group (67.7 years), and there was a slightly higher proportion of females in the CMM + mPNS group (66.7%) compared to the CMM alone group (52.2%). In terms of racial distribution, White participants constituted the majority in both groups (86.7% in CMM + mPNS and 95.7% in CMM alone). Black or African American participants represented 6.7% in the CMM + mPNS group and 4.3% in the CMM alone group, while 3.8% of participants did not report their race. Baseline vital sign measurements revealed that on average the participants were within normal ranges for body temperatures, blood



**Figure 1** Trial Profile. \*18 participants crossed over to mPNS treatment on day 90, and one participant crossed over after day 90 but before day 120 for a total of 19 participants in the Crossover group.

**Abbreviation:** CMM, conventional medical management.

pressures, and heart rates. Median body weight in both groups was slightly above average, with a median BMI of 30.1 in the CMM + mPNS group and 31.0 in the CMM alone group.

By Day 90, 22 participants (71.0%) in the CMM + mPNS group were found to be pain responders, compared to 3 participants (13.0%) in the CMM group, yielding a statistically significant difference of 57.9% (p-value of <0.0001) and

**Table 2** Participant Demographics and Baseline Characteristics

	<b>CMM + mPNS (N = 30)</b>	<b>CMM Alone (N = 23)</b>
Age, years		
Median (Range)	60.0 (35.1, 75.5)	67.7 (29.5, 74.0)
Sex, n (%)		
Male	10 (33.3%)	11 (47.8%)
Female	20 (66.7%)	12 (52.2%)

(Continued)

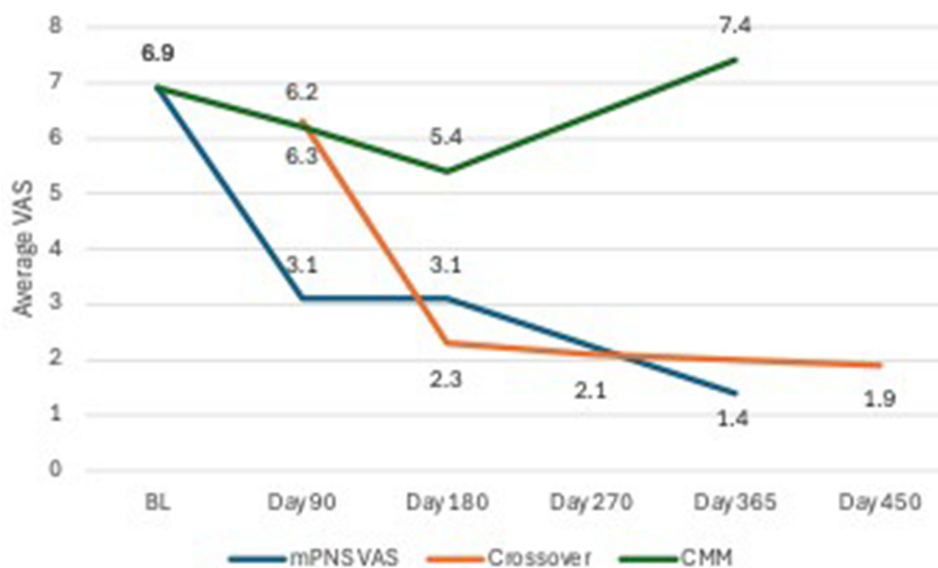
**Table 2** (Continued).

	<b>CMM + mPNS (N = 30)</b>	<b>CMM Alone (N = 23)</b>
Race, n (%)		
White	26 (86.7%)	22 (95.7%)
Black or African American	2 (6.7%)	1 (4.3%)
Not Reported	2 (6.7%)	0 (0%)
Ethnicity, n (%)		
Hispanic or Latino	2 (6.7%)	0 (0%)
Not Hispanic or Latino	26 (86.7%)	23 (100.0%)
Not Reported	1 (3.3%)	0 (0%)
Unknown	1 (3.3%)	0 (0%)
Vital signs and body size, median (range)		
Height (cm)	167.6 (142.2, 193.0)	172.7 (154.9, 195.6)
Weight (kg)	90.7 (47.6, 150.1)	94.3 (56.7, 125.6)
BMI (kg/m <sup>2</sup> )	30.4 (17.0, 44.9)	31.0 (21.6, 41.5)
Body temperature	98.0 (96.2, 99.2)	98.0 (97.1, 98.7)
Systolic blood pressure (mmHg)	119.0 (64.0, 175.0)	129.0 (61.0, 161.0)
Diastolic blood pressure (mmHg)	85.0 (57.0, 165.0)	82.0 (61.0, 160.0)
Heart rate (bpm)	77.5 (52.0, 99.0)	77.0 (56.0, 110.0)

a Cohen's  $h$  effect size of 1.3. On average, pain scores reduced from baseline by 50% ( $-3.81$ ; SD: 2.18) in the CMM + mPNS group, compared to a reduction of only 7% ( $-0.70$ ; SD: 2.16) in the CMM alone group ( $p < 0.0001$ ). Only one participant in each group initiated new pain medication, and only one participant in the CMM alone group reported an increase in pain medication use. After Day 90, no participants reported starting new pain medication or increasing pain medication use. However, no participants in either analysis set experienced a reduction in MEDD.

By Day 365, 94% of participants (15/16) were found to be pain responders in the CMM + mPNS group, as well as 69.2% (8/13) of participants in the Crossover group. Of these, a profound ( $>80\%$ ) reduction of pain was experienced by 62.5% of participants in the CMM + mPNS group, and 38.5% in the Crossover group. Changes in pain from baseline to Day 365 were also notable, with a 78.3% reduction of pain (mean score of 1.43; SD: 2.41) within the CMM + mPNS group, and a 68.2% reduction in pain (mean score of 1.86; SD: 1.97) in the Crossover group. In contrast, the two remaining participants in the CMM alone group exhibited a slight increase in pain levels, with a mean pain score of 7.40 (SD: 1.27) by the end of the study (Figure 2).

Mean EQ-5D-3L scores showed improvements by Day 365 for both CMM + mPNS and Crossover participants (Table 3). The CMM + mPNS group reached a mean score of 0.79 (SD: 0.21), resulting in an increase of 49.9% from baseline (mean difference: 0.26; SD: 0.24). The Crossover group had a mean score of 0.87 (SD: 0.17), with an increase of 40.4% from baseline (mean difference: 0.25; SD: 0.25). Reductions were also seen between baseline and the end of the study in the PDI scores for the CMM + mPNS group, with a mean difference of  $-25.19$  (SD: 15.66). Within the Crossover group, mean change in PDI from baseline to end of study was  $-15.08$  (SD: 11.95). Changes in pain from baseline through Day 365 were assessed using the PGIC with the categories of "much better", "a little better", "no change", "a little worse", and "much worse". Improvement in pain symptoms was defined as the proportion of subjects



**Figure 2** Average VAS Pain Scores at Baseline through Day 365.

who reported responses of either “much better” or “a little better” on the PGIC. At Day 365, 93.8% of CMM + mPNS participants and 92.3% of Crossover participants reported improvement on the PGIC. Patient satisfaction was defined as patients who reported being “very satisfied” or “satisfied” with treatment. At Day 365, 93.8% of CMM + mPNS participants and 92.3% of Crossover participants reported satisfaction with therapy compared with 0% in the CMM group. Of the participants who reported improvements in pain levels, 81.3% and 84.6% of participants in the CMM + mPNS and Crossover groups reported feeling “much better”, respectively (Table 3).

Treatment-Emergent adverse events (AEs) were reported by seven participants (20%) in CMM + mPNS, three (10.0%) in CMM alone, and five (26.3%) Crossover participants. The AEs were considered to be treatment-related in three (8.6%) CMM + mPNS participants, and two (10.5%) Crossover participants. No AEs led to withdrawal and no adverse device effects were reported in either group. The treatment related adverse events for mPNS were mild skin irritation, mild cramping, and/or slight, short-term increases in pain around the treatment area. No serious AEs were reported in the CMM + mPNS or Crossover groups. One serious AE (death) was reported in the CMM alone group (Table 4), but this was due to respiratory failure of a subject who contracted COVID-19.

**Table 3** Secondary Endpoints: Changes From Baseline to Day 365 of Patient-Reported Outcomes

	<b>CMM + mPNS</b>	<b>Crossover<sup>a</sup></b>
EQ-5D-3L (Mean change since baseline (SD))	0.26 (SD: 0.24)	0.25 (SD: 0.25)
PDI (Mean change since baseline (SD))	-25.19 (15.66)	-15.08 (11.95)
Improvement in PGIC since baseline (n (%))	15 (83.8%)	12 (92.3%)

**Notes:** <sup>a</sup>Unlike other measures which were collected from subjects at Day 0, Day 90, and end of study, PDI was collected at Day 0 and end of study (Day 365 for CMM-only and CMM + mPNS, Day 450 Crossover) only. Therefore, the evaluation period for PDI is longer in crossover subjects than in CMM-only and CMM + mPNS subjects.

**Abbreviations:** EQ-5D-3L, European Quality of Life 5 Dimensions 3 Level; PGIC, patient global impression of change; PDI, pain disability index.

**Table 4** Summary of Adverse Events Through End of Study, SAF Population

	<b>CMM + mPNS (N = 35) n (%)</b>	<b>CMM Alone (N = 30) n (%)</b>	<b>Crossover (N = 19) n (%)</b>
<b>Treatment-Emergent AE</b>	7 (20.0%)	3 (10.0%)	5 (26.3%)
Treatment-related AE <sup>b</sup>	3 (8.6%)	0 (0.0%)	2 (10.5%)
<b>Non-Treatment-Emergent AE</b>	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Serious Adverse Events</b>	0 (0.0%)	1 (3.3%)	0 (0.0%)
AE leading to death	0 (0.0%)	1 (3.3%)	0 (0.0%)
AE leading to withdrawal	0 (0.0%)	0 (0.0%)	0 (0.0%)
Device-related adverse events	0 (0.0%)	0 (0.0%)	0 (0.0%)

**Notes:** <sup>b</sup>Includes possibly related and definitely related AEs. CMM Alone events include the events from subjects remaining in CMM alone and the events before crossover from crossover subjects. Crossover events include the events after crossover from crossover subjects.

## Discussion

The initial SEAT study was the first multi-center, randomized controlled trial demonstrating the superiority of mPNS and CMM versus CMM alone. Pain responder rate, in this study was significantly higher in mPNS plus CMM group when compared to the CMM study group. In addition, changes in functional capacity and patient satisfaction, as measured by EQ-5D-3L and PGIC, suggested a great benefits to subjects who used mPNS.<sup>10</sup> When compared to CMM, mPNS provided a 71% responder rate (>50% neuropathic pain reduction).

In this study we showed that durable pain management was maintained for a period of one year. It is critical to emphasize that such long-term improvements are comparable to results seen with temporary implants,<sup>11,12</sup> or even with permanent invasive peripheral nerve stimulation system implantats.<sup>13,14</sup> In the SEAT study pain reduction was achieved with no risk to patients, using a non-invasive device and without requirements for an expensive procedure room, equipment, imaging, sterility and particularly implant trained physician and team to complete the procedure. It is important to understand that to utilize a traditional PNS therapy a positive response to a trial period with the device is required. This trial involves a temporary system which is implanted for a week to determine if the patient will benefit from the therapy prior to full surgical implant. Even though placement is temporary, electrode implantation carries surgical risks (eg bleeding, nerve damage and infection). In contrast, mPNS which is noninvasive with no implants and does not require a trial period.

Although PNS for mononeuropathy has been studied,<sup>9–15</sup> high-quality, prospective randomized studies are lacking. Design of this randomized prospective study is pragmatic as it compares mPNS when used with CMM to CMM itself. Numerous studies established prospective outcomes of conservative therapeutic approaches that frequently involve membrane stabilizers, antidepressants, opioids, topical medications, infusions, injections and denervations. Here we showed, using this elegant design, that initiation of mPNS makes a clinically meaningful difference short term (90 days)<sup>10</sup> and now long-term (1 year) compared to optimized CMM.

The majority of subjects (94%) were determined to be pain responders in the CMM + mPNS group at 1 year and about 70% of subjects in the Crossover group were also pain responders. Of these, a profound (>80%) reduction of pain was experienced by 62.5% of participants in the CMM + mPNS group, and 38.5% in the Crossover group. Such difference in outcomes between an initial patient cohort treated with mPNS and crossover group can be explained by the crossover group having a lower baseline due to the CMM control before crossover and the relatively small sample size of the treatment and crossover groups. In addition, if a medical study utilizing a crossover design shows a lesser response in the crossover group compared to the originally treated group, several factors could be at play. Differences in outcomes between an initial patient cohort treated with mPNS and crossover group may be explained by a sequence order effect or by regression to the mean effect. It is unlikely that there was any washout or carryover effect manifesting in this study design.

Profound improvements in Quality of Life (as measured by EQ-5D-3L and PGIC) followed improvements in pain scores and were maintained throughout 1-year follow-up time interval. The mPNS treated group maintained similar and not significantly different improvements at 1 year (see Figure 2) that we found previously during the short-term (3 months) analysis.<sup>10</sup>

Traditional percutaneous PNS frequently affects smaller fibers and may activate a varying and smaller proportion of large diameter fibers directly related to stimulation strength, type of electrode, distance to nerve fiber and its diameter. Remote selective targeting is therefore limited by unwanted fiber activation, using mPNS avoids some of the problems related to limited fiber recruitment associated with mono or bipolar conventional PNS.<sup>16</sup>

This study extends the research of mPNS<sup>10</sup>) offering a noninvasive treatment option for neuroma-related neuropathic pain conditions. Randomized controlled studies are required in further validating the efficacy of this treatment modality. Additional studies are also needed to assess the underlying electrophysiological mechanisms of the observed analgesic benefit.

A potential limitation of the Study is related to the observed subject attrition post-Day 90. The initial Study design did not provision for CMM crossover at Day 90. Crossover was implemented in a Protocol revision IRB-approved in July 2022. Before crossover, 2/6 (33.3%) of CMM subjects completed Day 365, whereas, after Crossover, 13/18 (72.2%) of CMM subjects completed Day 365 of mPNS+CMM after crossover, a large increase in retention rate. Another feature implemented in the July 2022 Protocol revision was an increased stipend implemented as a method to enhance subject retention. Before the stipend increase, only 3/14 (21.4%) of the mPNS+CMM subjects completed Day 365. After the stipend increase, 13/17 (76.5%) of the mPNS+CMM subjects completed Day 365, confirming the effectiveness of this countermeasure. It should also be noted that the COVID-19 pandemic had an impact on subject retention as well.

The underlying mechanisms of mPNS seem to be confirmed by this data. The powerful modulation of the A-beta suppressive fibers caused by mPNS is reflected in the markedly reduced pain scores. The durability of the pain relief over the 1-year period seems to be support the hypothesis of Deer et al regarding peripheral reconditioning of the central nervous system by peripheral nerve stimulation. The type of field generated by mPNS is drastically different than electrical fields generated along linear electrodes. mPNS delivers biphasic magnetic pulses at low frequencies between 0.2 to 5Hz, with typical application at 0.5Hz that induce powerful electrical fields in the nerve bundles located at the center of the waveform 10.

A magnetic field has greater penetration and spread than the diffuse non focused electrical field. Another important MOA in magnetic fields is their ability to induce an initial neuronal blockade.<sup>17,18</sup> This sensory blockade produces immediate results in approximately 60–75% of patients, even those who have suffered with neuropathic pain for decades.<sup>10</sup> It appears to further enhance the peripheral reconditioning of the central nervous system.

Opportunities to research mPNS further include investigating other forms of neuropathy (chemotherapy induced neuropathic pain for example) and understanding the health economic impact that mPNS could have, especially as related to the more invasive treatment modalities (SCS for example). With regard to health economic outcomes and understanding the comparison in incremental cost utility, there is not only the direct cost of the treatment to consider but also the downstream impacts regarding device explanation, infection and other impacts to the subjects. A longer study period would provide the opportunity to study those outcomes more thoroughly.

## Data Sharing Statement

The Principal Investigator takes responsibility for the integrity of the data and the accuracy of the data analysis, and has full access to all the data in the study. The deidentified participant outcome data supporting the findings of this study are available from the Principal Investigator in spreadsheet form on written request for 1 year post-publication.

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This study and its results have been presented and/or accepted as poster and platform abstracts at the American Society of Pain and Neuroscience 2024 Meeting in Miami Beach FL'

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Neuralace Medical.

## Disclosure

JCR owns stock options for Neuralace Medical and receives royalties or licenses from Eminent Spine from the design of SI joint screws. JCR receives support for attending the ASPN annual meeting from Eminent Spine, and receives consulting fees from Vertos Medical, Eminent Spine and Abbott Spine. JCR receives payments for acting as an expert witness in several court cases. SL received research grants from Avanos, Averitas Pharma, Nevro, Presidio, SPR Therapeutics and Neuralace Medical to his parent company (National Spine and Pain Centers). SL receives consulting fees from Abbott, Avanos, Averitas Pharma, Biotronik, Boston Scientific, Medtronic, Nalu Medical, NeuroOne, PainTeq, Presidio, Saluda, Stryker, SPR Therapeutics. SL was a past president of the New Jersey Society of Interventional Pain Physicians (NJSIPP) and is the vice-president elect of the American Society of Pain and Neuroscience (ASPN). LK receives consulting fees and payments or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Nevro, Avanos, Saluda, Nalu, Man and Science, Biotronik, Medtronic and Neuralace Medical. LK is also on the advisory board of Avanos, Man and Science, Nevro, Presidio, PainTeq, and Neuralace Medical. MB receives consulting fees from Neuralace Medical. The authors report no other conflicts of interest in this work.

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