OPEN ACCESS

# Clinical study of a micro-implantable pulse generator for the treatment of peripheral neuropathic pain: 3-month and 6-month results from the COMFORT-randomised controlled trial

John Hatheway ,[1] Alexander Hersel,[2] Jonathan Song,[3] Mitchell Engle,[4] Genaro Gutierrez,[5] Vishal Khemlani,[6] Leonardo Kapural,[7] Gregory Moore,[8] Reginald Ajakwe,[9] Drew Trainor,[10] Jennifer Hah,[11] Peter S Staats,[12] Paul Lynch,[13] James Makous,[14] Gary Heit,[15] Shilpa Kottalgi ,[16] Mehul J Desai [17]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/rapm-2023-105264).

For numbered affiliations see end of article.

**Correspondence to**
Shilpa Kottalgi, Nalu Medical Inc, Carlsbad CA 92008, California, USA;
skottalgi@nalumed.com

Gary Heit passed away in February 2023.

Received 3 January 2024
Accepted 15 May 2024



**To cite:** Hatheway J, Hersel A, Song J, *et al*. *Reg Anesth Pain Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/rapm-2023-105264

## ABSTRACT

**Background** We report the results from the first large, postmarket, multicentre, randomised controlled trial (RCT) evaluating peripheral nerve stimulation (PNS) for the treatment of chronic peripheral pain with a micro-implantable pulse generator (micro-IPG).

**Methods** Subjects meeting eligibility were randomised (2:1) to either the active arm receiving PNS and conventional medical management (CMM) or the control arm receiving CMM alone. Treatments were limited to the following areas: lower back, shoulder, knee and foot/ankle.

**Results** At 6 months, the active arm achieved an 88% responder rate with a 70% average reduction in pain. At the 3-month primary endpoint, the active arm achieved an 84% responder rate with an average pain reduction of 67% compared with the control arm, which achieved a 3% responder rate with an average pain reduction of 6%. Both responder rate and pain reduction in the active arm were significantly better than in the control arm ($p<0.001$). A majority of patient-reported outcomes also reached statistical significance. There have been no reports of pocket pain and no serious adverse device effects. 81% of subjects found the external wearable component of the PNS system to be comfortable.

**Conclusions** This study successfully reached its primary endpoint—the active arm achieved a statistically significant superior responder rate as compared with the control arm at 3 months. These RCT results demonstrated that PNS, with this micro-IPG, is efficacious and safe. This ongoing study will follow subjects for 3 years, the results of which will be reported as they become available.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Peripheral nerve stimulation (PNS) has been widely used for over 50 years to treat intractable chronic pain of peripheral nerve origin.

⇒ However, there is a paucity of data from randomised clinical trials. A previous PNS randomised controlled trial (RCT) showed borderline-positive outcomes.

### WHAT THIS STUDY ADDS

⇒ This study showed, through a well-controlled RCT using validated outcome instruments, that PNS therapy delivered by a micro-implantable pulse generator device significantly reduced pain and improved functional outcomes in over 80% of subjects treated.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The outcomes of this study provide a basis for clinical evidence in support of patient access to PNS therapy, as provided by the study device.

⇒ The results presented here provide clinical confidence in the application of PNS therapy to appropriate patients.

## INTRODUCTION

Peripheral nerve stimulation (PNS) is an established modality for the treatment of chronic peripheral neuralgia/neuropathy.[1] The prevalence of neuropathic pain may be as high as 10% in the general population.[2] When more conservative methods (eg, physical therapy or over-the-counter pain medications) fail, then second-line therapies include nerve blocks and prescription medications. The last line of therapies involves PNS, which has been used as a treatment for chronic pain since the 1960s[3] and now is supported by a growing body of evidence. We report here the results from the first large, postmarket, multicentre, on-label, randomised control trial (RCT) documenting the effectiveness and safety of PNS and conventional medical management (CMM) versus CMM alone in the treatment of chronic peripheral neuropathic pain with a micro-implantable pulse generator (micro-IPG) PNS system.

The device evaluated in this RCT is an FDA-cleared (K183579 and K191435) system with a battery-free micro-IPG, a volume of $<1.5\,cm^3$ and an 18-year service life (Nalu Neurostimulation System, Carlsbad, California, USA). The system is powered by a small, externally worn battery (therapy disc (TD)). Unlike other PNS systems, the micro-IPG system allows for a temporary trial lead

placement. It also offers a broad menu of therapeutic stimulation parameters and waveforms. The system software is upgradeable without micro-IPG replacement (see Kalia *et al*[4] for a detailed device description).

## METHODS

The COMFORT (Clinical Study Of A Micro-Implantable Pulse Generator FOR the Treatment of Peripheral Neuropathic Pain) study was approved by the Institutional Review Board and conducted in compliance with local regulations and standards for good clinical practice. The study is registered on ClinicalTrials.gov (NCT05287373; date of registration: 08 February 2022; https://classic.clinicaltrials.gov/ct2/results?cond=&term=NCT05287373&cntry=&state=&city=&dist=).

Subjects who met the inclusion/exclusion criteria were randomised at 12 pain management centres across the USA, with enrollment commencing on 23 February 2022 and being completed on 29 March 2023. Full inclusion and exclusion are available on ClinicalTrials.gov. In brief, inclusion criteria included subjects diagnosed with one or more of the conditions listed below in the lower back, shoulder, knee or foot/ankle—postsurgical/post-traumatic peripheral neuralgia, including pain due to peripheral nerve injury; this was updated to include post-surgical scar formation, nerve entrapment, mononeuropathy and osteoarthritic pain, to align with the standard of care for PNS. Exclusion criteria included complex regional pain syndrome, peripheral neuralgia of metabolic origin and postherpetic origin; the subject is on ≥90 morphine mg equivalents per 24 hours.

The primary efficacy measure was the numeric rating scale (NRS) pain score captured in the Brief Pain Inventory Question 5 (BPI-Q5) from the target area of peripheral pain. Secondary outcome measures included the following patient-reported outcomes (PROs): Patient Global Impression of Change (PGIC), Brief Pain Inventory Short Form (BPI-SF), quality-of-life metric (EuroQoL 5 dimension 5 level (EQ-5D-5L)), Beck Depression Inventory (BDI) and Oswestry Disability Index (ODI). Patient safety, satisfaction, device comfort, usability and subject compliance with the therapy were also tracked.

The study design was intended to mimic real-world clinical practice as closely as possible.

Consented subjects received baseline evaluations per protocol and standard clinical practice. Eligible subjects were then randomised into one of two arms: the active arm, which received PNS and CMM, and the control arm, which received CMM alone (figure 1). Allocation was concealed prior to randomisation, which was performed using a random permuted block design (block size of three) with a 2:1 allocation ratio (active vs control). Randomisation was stratified by investigational site and assigned via a centralised electronic system. The randomisation sequence was generated by SAS (V.9.4, SAS Institute, Cary, North Carolina, USA).

Subjects randomised to the control arm continued to receive CMM alone for the next 3 months. Upon completion of the 3-month primary endpoint, subjects in the control arm were given the option to crossover into the active arm. Crossover subjects continued under the same follow-up visit schedule as those in the active arm. CMM was defined as the best standard of care for each individual subject, as determined by the investigator. CMM was standardised across institutions in both the active and control arms. See table 1 for a list of CMM administered during the study. Results from the crossover will be presented in a subsequent publication.

Subjects randomised to the active arm underwent a temporary trial procedure per standard of care. Subjects needed to achieve ≥50% reduction in pain during the trial period (a 'responder') in order to be eligible for a permanent implant (52 of 57 clinically successful trials yielding a 91% success rate). Those who realised <50% improvement were considered trial failures and were exited from the study. The responders were implanted with a permanent system per standard clinical practice and

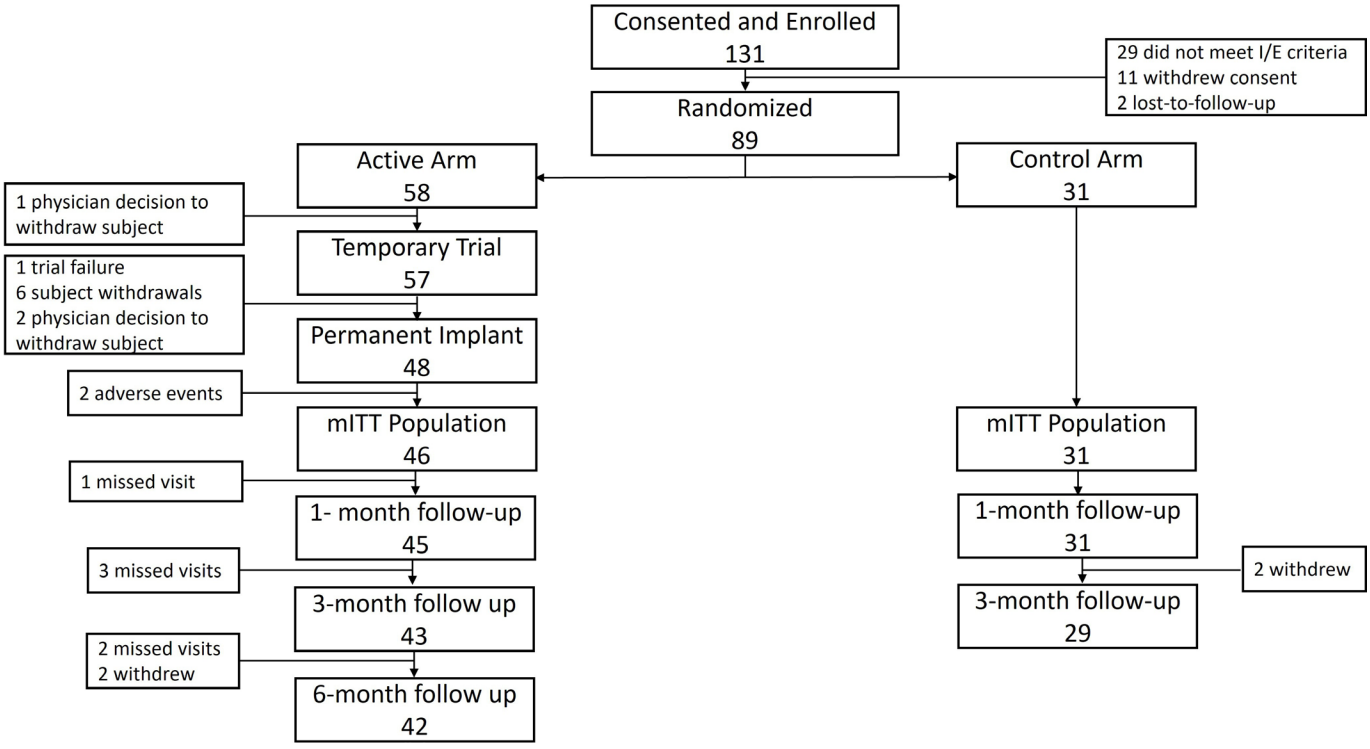



**Figure 1** Subject disposition from consent to the 6-month endpoint. mITT, modified intention-to-treat.

**Table 1** Subject demographics and baseline characteristics

| Characteristics | Mean±SD (N) (Min, Max) or % (N) | | |
|---|---|---|---|
| | Total modified intention-to-treat population | Active arm (PNS+CMM) | Control arm (CMM only) |
| Age (in years) | 57.4±11.8 (77) (21–77) | 57.6±11.5 (46) (21–77) | 57.03±12.5 (31) (29–76) |
| Female | 70% (54/77) | 70% (32/46) | 71% (22/31) |
| Male | 30% (23/77) | 30% (14/46) | 29% (9/31) |
| Body mass index | 33.0±7.8 kg/m$^2$ (77) (20.5–64.3) | 33.3±8.3 kg/m$^2$ (46) (21.4–64.3) | 32.4±7.1 kg/m$^2$ (31) (20.5–49.5) |
| Years since diagnosis | 5.0±5.6 (77) (0.6–27.8) | 4.1±4.8 (46)(0.6–23) | 6.3±6.5 (77)(0.6–27.8) |
| Areas of pain | | | |
| Low back (superior cluneal nerve) | 49.4% (38/77) | 52.2% (24/46) | 45.2% (14/31) |
| Knee (genicular, peroneal and sciatic nerves) | 20.8% (16/77) | 17.4% (8/46) | 25.8% (8/31) |
| Shoulder (suprascapular and axillary nerves) | 13.0% (10/77) | 15.2% (7/46) | 9.7% (3/31) |
| Foot/ankle (sciatic, tibial, sural and peroneal nerves) | 16.9% (13/77) | 15.2% (7/46) | 19.4% (6/31) |
| Opioid usage | | | |
| Opiates at screening | 53% (41/77) | 46% (21/46) | 65% (20/31) |
| Morphine milligram equivalents* | 15.1±22.4 (77) (0–83) | 12.7±20.5 (46) (0–76) | 18.8±24.7 (31) (0–83) |
| CMM† | | | |
| Oral medications | 99% (76/77) | 98% (45/46) | 100% (31/31) |
| Topical medications | 39% (30/77) | 41% (19/46) | 35% (11/31) |
| Physical therapy | 58% (45/77) | 61% (28/46) | 35% (17/31) |
| Psychological therapy | 10% (8/77) | 9% (4/46) | 13% (4/31) |
| Acupressure/acupuncture | 14% (11/77) | 11% (5/46) | 19% (6/31) |
| Nerve blocks | 45% (35/77) | 43% (20/46) | 48% (15/31) |
| Epidural steroid injections | 30% (23/77) | 28% (13/46) | 32% (10/31) |
| Others (prior short-term PNS, chiropractic, bracing, radio frequency ablation, trigger point injections, transcutaneous nerve stimulation, ice/heat and massage) | 53% (41/77) | 52% (24/46) | 55% (17/31) |

*No statistical difference detected between the groups at baseline.
†Subjects used one or more of the above at the time of screening.
CMM, conventional medical management; PNS, peripheral nerve stimulation.

were programmed with paresthesia-based and paresthesia-independent programmes. Subjects were then followed at prespecified time points up to 36 months; however, the current analysis was focused on the 3-month primary endpoint plus 6-month outcomes, as the study is ongoing.

Aside from the temporary trial and micro-IPG implant, both study arms were treated equally to ensure clinical equipoise. PROs and adverse events (AE) were captured at each of the follow-up visits.

Following the implant procedure, the system was programmed for optimal pain relief per standard clinical practice. The programming was performed by clinical personnel from the study sponsor, under the direction of a study physician. All programming was consistent with the device labelling and in a manner typically applied to patients outside of the clinical study. There were no off-label investigational devices or programming parameters used in this study. Interestingly, nearly all the programmes for the patients used complex programming, similar to the capabilities of spinal cord stimulation systems (pulse widths of ≥500 µs, frequencies ≥500 Hz, use of more than two electrodes, multiarea, cross-lead, current steering and/or proprietary waveforms). Approximately one-third used pulse widths ≥500 µs, frequencies ≥1000 Hz and/or >2 electrodes (anodes/cathodes combinations). A majority of programmes were multi-area, cross-lead, current steering and/or proprietary waveforms. Subjects were given a choice of up to eight sub-paresthesia and supra-paresthesia stimulation programmes, which they could cycle through based on the therapeutic benefit.

## Statistical analysis

Primary endpoint analysis was carried out on the modified-intent-to-treat (mITT) population, as prespecified in the statistical analysis plan. The mITT population is defined as 'all randomised subjects receiving a permanent implant and having an implant at the time of analysis in the active arm and all randomised subjects in the control arm'. The primary effectiveness endpoint was the percentage of responders (responders were defined as ≥50% reduction in pain relative to baseline) at 3 months captured in the NRS-BPI-Q5 for their primary area of pain relative to baseline. Comparisons were made between randomised arms. Missing data were assumed to be missing completely at random. Results were reported as mean±SD for continuous variables and as a percentage (count) for categorical variables, unless otherwise noted. Comparisons of responder rates between the active arm and control arm were conducted by a two-sample t-test; within-arm comparisons were conducted using the Wilcoxon signed-rank test. P values of $<0.05$ were regarded as statistically significant. For all outcomes, per cent reduction is calculated as a paired analysis within each subject and reported as mean±SD. Analyses were conducted using SAS.

The sample size for the study was based on power requirements for the primary effectiveness endpoint. A sample size of 87 randomised subjects was calculated based on a two-sample exact binomial test with a two-sided 0.05 alpha level, providing 90% power for a difference in responder rate between the arms.

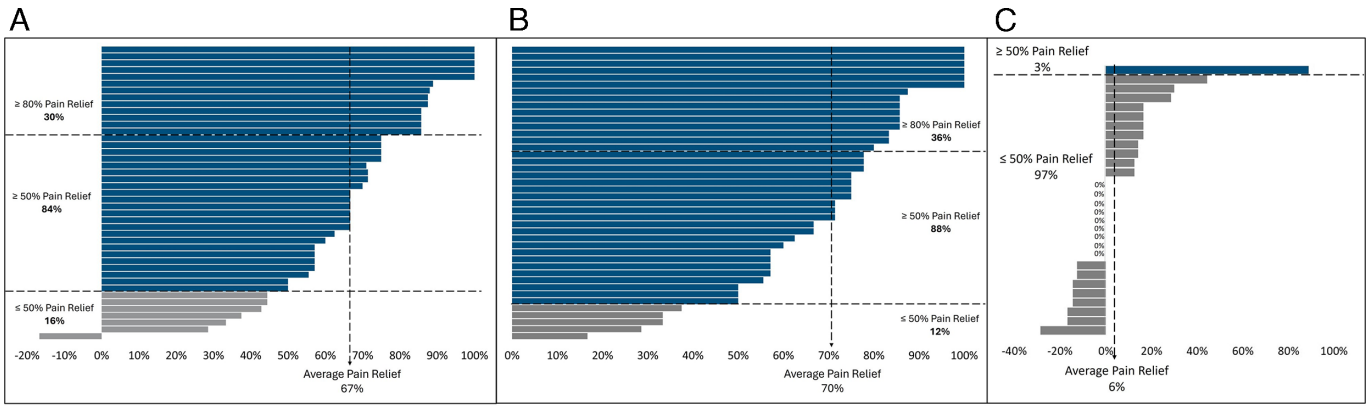



**Figure 2** Tornado plot. (A) Active arm at 3 months, (B) active arm at 6 months and (C) control arm at 3 months, showing per cent pain relief in each study subject. Responders were subjects with ≥50% pain reduction compared with their baseline NRS pain score. High responders were subjects with ≥80% pain reduction compared with their baseline pain score. NRS, numeric rating scale.

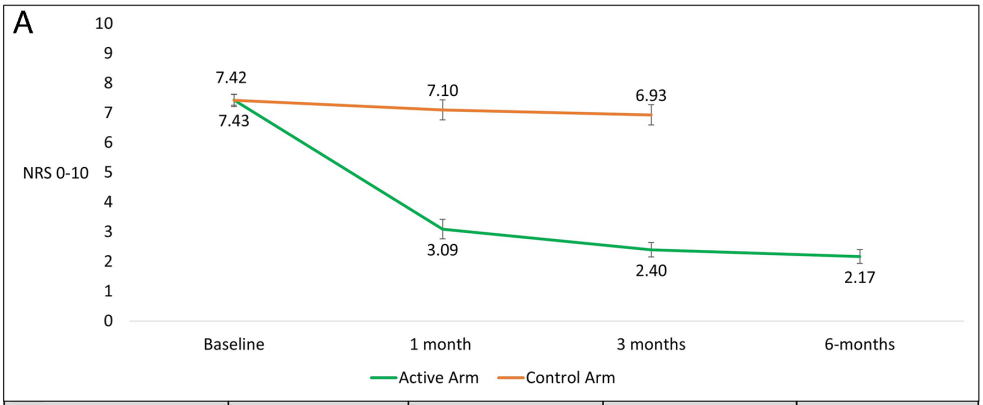
## RESULTS

131 subjects consented. Of these, 89 subjects were randomised to the active arm (58 subjects) or the control arm (31 subjects). Of these, 12 subjects exited early in the active arm and were not included in the mITT population. The mITT population included 46 active arm subjects and 31 control arm subjects. At 3 months, three subjects in the active arm missed the visit and two subjects in the control arm withdrew. The details of the final subject disposition are shown in figure 1.

The demographic distribution of the subjects is detailed in table 1. 49.4% (38/77) of subjects had chronic pain in the lower back, 20.8% (16/77) in the knee, 16.9% (13/77) in the foot/ankle and 13% (10/77) in the shoulder. Targeted nerves are listed in table 1.

The responder rate was 84% (36/43) at 3 months and 88% (37/42) at 6 months in the active arm compared with 3% (1/29) in the control arm (figure 2; p<0.001). Subjects in the active arm achieved a 67% improvement at 3 months and a 70% improvement at 6 months in pain as compared with baseline (p<0.001), whereas the control arm achieved a 6% improvement in pain. A comparison between the responder rates in the two arms at 3 months (primary endpoint) was statistically significant at p<0.001 (figure 3). 30% (13/43) of active arm subjects and 3% (1/29) of control arm subjects were high responders, with ≥80% pain improvement from baseline (figure 3).

The PROs are shown in table 2 in the following areas: BPI-SF (both interference and severity), EQ-5D-5L, BDI and ODI. Each of these measures demonstrated a statistically significant




| B | Active Arm (43) 3-months | Control Arm (29) 3-months | p-value Active vs Control | Active Arm (42) 6-months |
|---|---|---|---|---|
| Responder Rate | 84% | 3% | p < 0.001 | 88% |
| % Pain Relief | 67% | 6% | p < 0.001 | 70% |
| High Responders | 30% | 3% | p < 0.05 | 36% |

**Figure 3** Mean NRS pain scores (BPI-Q5) and responder rates at 3 and 6 months. (A) Pain scores captured in the office at baseline and at 1 month, 3 months and 6 months for active and control arms. The mean per cent reduction in pain was statistically significant in the active arm compared with the control arm at 1, 3 and 6 months (p<0.001). Each data point represents mean±SEM. (B) Responder rates (≥50% improvement) and high responder rates (≥80% improvement) were statistically better in the active arm versus the control arm, at p<0.001 and p<0.05, respectively. Per cent pain reduction was also significantly better in the active arm versus the control arm at p<0.001. The sample size (N) is shown in parentheses. BPI-Q5, Brief Pain Inventory Question 5; NRS, numeric rating scale.

**Table 2** Patient reported outcomes (PRO) at 3 and 6-months. BPI, EQ-5D-5L, BDI and ODI.

| | Active arm | | | Control arm | |
|---|---|---|---|---|---|
| | Baseline | 3 months | 6 months | Baseline | 3 months |
| Assessment | Mean±SD (N) | Mean±SD (N) (% change) | Mean±SD (N) (% change) | Mean±SD (N) | Mean±SD (N) (% change) |
| BPI- severity | 6.69±1.51 (46) | 2.93±1.95 (42) (55%; p<0.001) | 2.65±1.43 (42) (59%; p<0.001) | 6.73±1.75 (31) | 6.41±1.79 (27) (2%; p=0.56) |
| BPI- Interference | 5.99±2.16 (46) | 2.32±2.05 (42) (58%; p<0.001) | 2.06±1.76 (41) (64%; p<0.001) | 6.12±1.88 (31) | 5.73±2.02 (27) (2%; p=0.60) |
| BDI | 11.87±9.48 (46) | 6.40±7.0 (43) (38%; p<0.001) | 4.74±5.57 (42) (48%; p<0.001) | 12.19±10.93 (31) | 9.0±7.86 (29) (13%; p=0.18) |
| EQ-5D-5L | 0.63±0.16 (46) | 0.78±0.13 (43) (40%; p<0.001) | 0.79±0.12 (40) (41%; p<0.001) | 0.59±0.12 (31) | 0.63±0.14 (29) (10%; p=0.02) |
| ODI | 42.8±13.3 (46) | 22.7±15.4 (43) (45%; p<0.001) | 22.0±15.3 (42) (46%; p<0.001) | 43.7±16.3 (31) | 40.0±17.9 (29) (7%; p=0.14) |
| **ODI categorical** | **% (N)** | **% (N)** | **% (N)** | **% (N)** | **% (N)** |
| Minimal | 2% (1) | 51% (22) | 57% (24) | 10% (3) | 14% (4) |
| Moderate | 50% (23) | 33% (14) | 29% (12) | 32% (10) | 41% (12) |
| Severe | 37% (17) | 16% (7) | 12% (5) | 45% (14) | 31% (9) |
| Crippled | 11% (5) | 0% (0) | 2% (1) | 13% (4) | 14% (4) |
| Bed bound | 0% (0) | 0% (0) | 0% (0) | 0% (0) | 0% (0) |

BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; EQ-5D-5L, EuroQoL 5 Dimension 5 Level, Quality-of-Life metric; ODI, Oswestry Disability Index; PRO, patient reported outcomes.

(p<0.001) improvement at 3 months and 6 months following device activation, whereas none of the PROs in the control arm yielded statistical significance at 3 months.

The PGIC was used to assess a subject's overall impression of change (better or worse) following treatment. 98% of active arm subjects reported an improvement at both 3 and 6 months, compared with only 14% (4/29), in the control arm (p<0.001) at 3 months. In the active arm, 58% (25/43) of subjects reported very much improved, 30% (13/43) reported much improved, and 9% (4/43) reported minimally improved. None of the active arms reported minimally worse, 2.3% (1) reported much worse, and none reported very much worse. In the control arm, no subjects (0%) reported very much improved, 7% (2/29) reported much improved, 7% (2/29) reported minimally improved, 69% (20/29) reported no change, 10% (3/29) reported minimally worse and 7% (2/29) reported much worse. Similar results were seen at 6 months in the active arm.

Subjects in the active arm were also asked to rate their overall satisfaction with the PNS system on a five-point Likert scale. 77% (33/43) of active arm subjects were very satisfied with the system; 21% (9/43) were satisfied, whereas one subject (2%) was very dissatisfied at 3 months. At 6 months, 71% (30/42) of active arm subjects were very satisfied with the system; 26% (11/42) were satisfied, whereas one subject (2%) was dissatisfied.

At 3 months, 43 subjects in the active arm reported their comfort ratings related to the device. 81% (35/43) reported that the wearable was very comfortable or comfortable. 91% (39/43) of subjects reported the device as very easy or easy to use. 81% (35/43) of subjects reported using the device for a full day. At 6 months, 79% (33/42) of subjects continued to report the device to be very comfortable or comfortable. 90% of subjects found the device to be very easy or easy to use and 76% (32/42) reported using it for a full day.

Subjects in both study arms continued their CMM regimen as needed. At 3 months, 88% (38/43) of active arm subjects and 100% (29/29) of control arm subjects reported continued use of oral medications. Other CMM reported at 3 months include topical medications (12), physical therapy (4), psychological therapy (4) and other treatments (11; bracing, chiropractic, water aerobics and removal of bursa); one control arm subject reported using a transcutaneous nerve stimulation unit. At 6 months, in the active arm, 90% (38/42) of subjects continued to take oral medications, 11 reported using topical medications, four underwent physical therapy, five were in psychological therapy and four subjects used a brace.

No unanticipated serious adverse device effects have been reported in the study to date. There were no serious AEs (SAEs) related to the device or procedure. No reports of pocket pain have been reported to date. All non-serious adverse device effects were resolved with no sequelae. Lead migration was reported in one patient, which resulted in a revision. One additional patient had swelling and induration without an infection, which resulted in revision. One patient had a lead fracture in the knee, which resulted in a revision. One patient had a mild infection at the implant site that resolved without sequelae following treatment with antibiotics (oral cephalexin 500 mg four times a day for 15 days). One patient had an IPG migration that was revised. Two other patients had infections postimplant; both had their devices explanted, the infections resolved and the subjects discontinued study participation. Seven non-device-related SAEs were reported in the active arm at the 6-month timepoint, all resolving with no sequelae. In the control arm, two non-SAEs were reported, which were not related to their current CMM regimen.

## DISCUSSION

The study was a success by meeting the primary endpoint. The 3-month responder rate was 84% with a 67% average pain reduction in the active arm, compared with a 3% responder rate and a 6% average pain reduction in the control arm (p<0.001). The results were maintained, where the responder rate at 6 months was 88% with a 70% pain reduction. The outcomes were consistent across the four areas of pain and the respective nerve targets included in the study. Favourable comfort, compliance and ease-of-use outcomes indicated that the wearable aspects of the system (see figure 4 for the system description) were well received by users. There was a strong safety profile

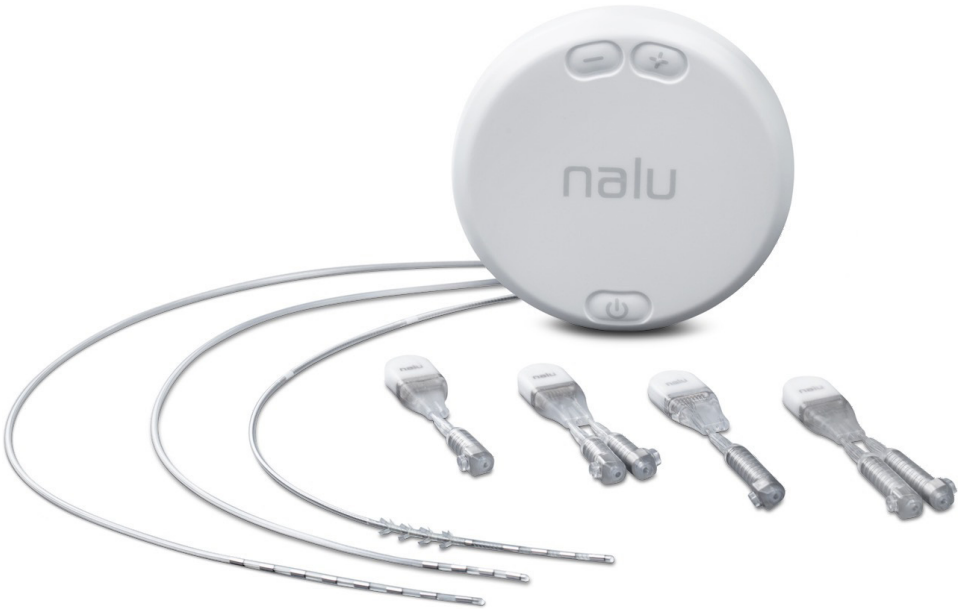



**Figure 4** Peripheral nerve stimulation system used during the course of this study. The Nalu system consists of a micro-implantable pulse generator (<1.5 cc) that is powered by a therapy disc worn over the implant with an adhesive clip or a limb cuff. Bidirectional telemetry allows for optimal therapy delivery. There were three lead configurations employed during this study: four-contact leads with tines, four-contact leads without tines and eight-contact leads without tines. In addition, there were four micro-IPG configurations: Single port for four-contact leads, dual port for four-contact leads, single port for eight-contact leads and dual port for eight-contact leads.

with a complete lack of serious adverse device events and no reports of pocket pain. Subsequent publications will report on the 1-year, 2-year and 3-year outcomes of these subjects.

The results of this RCT were significantly better than a separate PNS RCT with an older device (StimRouter, Bioventus).[5] In that study, the observed responder rates (30% responder rate criterion) were 38% in the active arm versus 10% in the control arm. The pain relief was 27% for the active arm versus 2.3% pain reduction in the control arm. These reductions in pain scores were smaller than seen in the current study, especially when the responder rate criterion is taken into account (ie, 30% vs 50%). If the 30% responder rate criterion was applied in the COMFORT study, instead of 50%, the responder rate would improve to 95% (41/43) in the active arm and to 10% (3/29) in the control arm.

The improvements in the COMFORT study were similar to or better than the prospectively collected values reported in the PNS literature. For example, Hassenbush *et al*[6] found a 63% (19/30) PNS responder rate (50% criterion) in Reflex Sympathetic Dystrophy/Chronic Regional Pain Syndrome (RSD/CRPS) with an average pain reduction of 59% (8.3±0.3 at baseline, prior to implant, to 3.5±0.4 at last follow-up; mean follow-up of 2.2±0.6 years). The target nerves were as follows: median/ulnar, radial, common peroneal and posterior tibial. In another study, Possover *et al*[7] demonstrated an 83% (19/23) PNS responder rate (50% criterion) in posthernia repair neuralgia, with an average pain reduction of 62% (8.1±8.1 at baseline to 3.1±2.8 postimplantation). The mean follow-up was 28.6±16.2 months. The target nerves were genitofemoral, ilioinguinal, iliohypogastric and lateral femoral cutaneous.

The outcomes reported here are also comparable to those reported in three separate retrospective studies. Eisenberg *et al*[8] studied 46 subjects with various forms of peripheral neuropathy and demonstrated a statistically and clinically significant improvement in pain scores following PNS ($p<0.001$). Law *et al*[9] demonstrated retrospective pain control in 13 of 22 (59%) traumatic peripheral neuropathic pain subjects out to 25 months post-PNS implant, and Schon *et al*[10] also demonstrated satisfactory pain reduction in 61% of lower extremity nerve injury pain in a retrospective study of 62 subjects.

The fact that the COMFORT study results are better than those of previous PNS studies cited here may be due in part to the advancement in processor technologies that allow for the miniaturised form factor of the micro-IPG while maintaining advanced programming capabilities that were lacking in the devices used in the other studies.

The lack of pocket pain in the COMFORT study is consistent with data from two other clinical studies investigating the same micro-IPG system for spinal cord stimulation, where the micro-IPG was placed in the lower back.[11 12] The reports in the literature of pocket pain associated with traditional IPGs can be as high as 64%.[13 14] Unlike large implants, which can be limited in their implant location, this micro-IPG is more versatile and can be placed in the location that best suits the subject, regardless of body mass index (BMI) (study BMI range: 20.5–64.3 kg/m$^2$) and can help avoid the need for leads crossing joints.

96% (126/131) of subjects who were screened liked or tolerated the wearable. The high satisfaction, comfort, compliance and usability scores reported here may be due to a unique patient-centric attribute of this micro-IPG system. Specifically, the 'Wear Assessment' ensures that the subject and the implanting physician agree upon the micro-IPG implant location and that the subject is comfortable with the external wearable. This process reduces the risk of revisions related to poor micro-IPG placement. Additionally, subjects had the opportunity to use the TD with a limb cuff and/or adhesive clip, regardless of the location of the micro-IPG implant. These favourable results are consistent with other studies involving the micro-IPG,[11 12] and they show the patient acceptability, comfort and usability of the system.

Limitations of this study include the fact that the control arm remained in CMM only for 3 months; a longer period was considered but was thought to be ethically problematic for those

subjects with significant pain. The prevalence of females over males was unanticipated (70% females), but the randomisation addressed potential bias, and this reflected the real-world population at the clinical sites.

## CONCLUSIONS

The study met the criterion for success—the active arm achieved statistical significance at the primary endpoint over the control arm in the responder rate. Treatment with this micro-IPG resulted in statistically significant improvement in pain (and in other PROs) relative to baseline values and between the active and control arms. The outcomes were consistent with, and in some cases superior to, results in the PNS literature for the treatment of pain associated with chronic peripheral neuropathy or neuralgia. There was a strong safety profile with no serious adverse device effects and no reports of pocket pain. Subjects also reported high ratings for comfort and ease of use while wearing the external components. The small size of this micro-IPG allowed it to be used in all four of the anatomic locations studied without regard to body habitus. The sponsor and investigators are dedicated to continuing the study and reporting the long-term outcomes when available.

**Author affiliations**
[1]Northwest Pain Care, Spokane, Washington, USA
[2]Pain Management and Injury Relief, Thousand Oaks, California, USA
[3]Arizona Pain Specialists, Scottsdale, Arizona, USA
[4]Institute of Precision Pain Medicine, Corpus Christi, Texas, USA
[5]Pain Specialists of America, Austin, Texas, USA
[6]Columbia Pain Management, Portland, Oregon, USA
[7]Center for Clinical Research, Carolinas Pain Institute, Winston-Salem, North Carolina, USA
[8]Pacific Sports and Spine, Eugene, Oregon, USA
[9]Comprehensive Spine & Pain Physicians, Burbank, California, USA
[10]Denver Spine and Pain Institute, Denver, Colorado, USA
[11]Division of Pain Medicine, Stanford University, Palo Alto, California, USA
[12]Premier Pain Ctr, Shrewsbury, New Jersey, USA
[13]US Pain Care, Scottsdale, Arizona, USA
[14]Makous Research, LLC, Carlsbad, California, USA
[15]Hue University of Medicine and Pharmacy, Hue, Thua Thien Hue, Viet Nam
[16]Nalu Medical Inc, Carlsbad, California, USA
[17]International Spine, Pain & Performance Center, Washington, District of Columbia, USA

**Acknowledgements** We would like to thank the COMFORT study investigators, subinvestigators and coordinators at the following US sites for their participation and support in this study: Arizona Pain Specialists, DBPS Research, LLC, International Spine, Pain & Performance Center, The Center for Clinical Research, Institute of Precision Pain Medicine, Northwest Pain Care, PS, Stanford University, Pacific Sports and Spine, Comprehensive Spine and Pain Physicians, Pain Management and Injury Relief, Pain Specialists of America and Columbia Pain Management, PC, University of Wisconsin, University of Iowa and University of Arkansas. We would also like to thank our statistician Ping-Yu Liu.

**Contributors** All authors either made a substantial contribution to the study concept, design, and/or analysis, or they enrolled at least one study subject. All authors approved the final version of the manuscript. SK is responsible for the overall content as the guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled decision to publish.

**Funding** This study was sponsored by Nalu Medical.

**Competing interests** GH is a consultant at Nalu Medical, Agitated Solutions, and a co-founder of Nesos. PS is a consultant for Nalu Medical, Saluda, SPR therapeutics and Medtronic. He is the Chief Medical Officer at electroCore. SK is an employee at Nalu Medical. JM is a consultant at Nalu Medical and owns stock in Nalu Medical. JH is a speaker and consultant for Nalu Medical. MJD consults for Avanos, Nalu, SPR Therapeutics; receives research support from Abbott, Avanos, Averitas, Mainstay, Nalu, Nature Cell, Saol, SPR Therapeutics and Vivex; and owns stock options in SPR Therapeutics, SynerFuse and Virdio.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by WCG IRB Tracking Number: 20215749. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information. Not Applicable.



**ORCID iDs**
John Hatheway http://orcid.org/0000-0002-9551-2150
Shilpa Kottalgi http://orcid.org/0000-0001-6686-3587
Mehul J Desai http://orcid.org/0000-0001-6870-9436

## REFERENCES

1 Slavin KV. History of peripheral nerve stimulation. *Prog Neurol Surg* 2011;24:1–15.
2 van Hecke O, Austin SK, Khan RA, *et al*. Neuropathic pain in the general population: a systematic review of Epidemiological studies. *Pain* 2014;155:654–62.
3 Wall PD, Sweet WH. Temporary abolition of pain in man science. *Science* 1967;155:108–9.
4 Kalia H, Pritzlaff S, Li AH, *et al*. Application of the novel Nalu Neurostimulation system for peripheral nerve stimulation. *Pain Manag* 2022;12:795–804.
5 Deer T, Pope J, Benyamin R, *et al*. Partial crossover study to assess the safety and efficacy of the novel Neuromodulation system in the treatment of patients with chronic pain of peripheral nerve origin. *Neuromodulation* 2016;19:91–100.
6 Hassenbusch SJ, Stanton-Hicks M, Schoppa D, *et al*. Long-term results of peripheral nerve stimulation for reflex sympathetic dystrophy. *J Neurosurg* 1996;84:415–23.
7 Possover M. Use of the LION procedure on the sensitive branches of the lumbar plexus for the treatment of intractable Postherniorrhaphy neuropathic Inguinodynia. *Hernia* 2013;17:333–7.
8 Eisenberg E, Waisbrod H, Gerbershagen HU. Long-term peripheral nerve stimulation for painful nerve injuries. *Clin J Pain* 2004;20:143–6.
9 Law JD, Swett J, Kirsch WM. Retrospective analysis of 22 patients with chronic pain treated by peripheral nerve stimulation. *J Neurosurg* 1980;52:482–5.
10 Schon LC, Lam PW, Easley ME, *et al*. Complex salvage procedures for severe lower extremity nerve pain. *Clin Orthop Relat Res* 2001;391:171–80.
11 Salmon J, Bates D, Du Toit N, *et al*. Early experience with a novel Miniaturized spinal cord stimulation system for the management of chronic intractable pain of the back and legs. *Neuromodulation* 2023;26:172–81.
12 Desai MJ, Raju T, Ung C, *et al*. Results from a prospective, clinical study (US-nPower) evaluating a miniature spinal cord Stimulator for the management of chronic, intractable pain. *Pain Physician* 2023;26:575–84.
13 Dietvorst S, Decramer T, Lemmens R, *et al*. Pocket pain and Neuromodulation: negligible or neglected *Neuromodulation* 2017;20:600–5.
14 Burke L, Desai MJ. Pocket pain following spinal cord Stimulator generator implantation: A narrative review of this under-reported risk. *Pain Pract* 2024;24:659–69.