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Clinical study of a micro-implantable pulse generator for the treatment of peripheral neuropathic pain: 12-month results from the COMFORT-randomized controlled trial

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ABSTRACT

Background There is paucity of data from randomized controlled trials supporting the use of peripheral nerve stimulation, a well-established therapy for the treatment of chronic pain. This study was undertaken, in part, to provide randomized controlled trial data in support of patient access to appropriate peripheral nerve stimulation therapy. The COMFORT study is the first large, postmarket, multicenter randomized controlled trials investigating the use of a Food and Drug Administration-cleared micro-implantable pulse generator (IPG) for treating chronic pain via peripheral nerve stimulation therapy.

Methods Consented, eligible subjects were randomized to either the active arm, which received peripheral nerve stimulation and conventional medical management, or the control arm, which received conventional medical management alone and were allowed to cross over to the active arm, after 3 months. Pain and patient-reported outcomes were captured. Therapy responders were subjects who achieved at least a 50% reduction in pain scores compared with baseline. We are reporting the 12-month results of this 36-month study.

Results At 12 months, the responder rate was 87% with a 69% average reduction in pain compared with baseline (7.5±1.2 to 2.3±1.7; p<0.001). Statistical significance was achieved for all patient-reported outcomes. There was an excellent safety profile with no serious adverse device effects or reports of pocket pain. A majority of subjects used unique programming options and found this device easy to use and comfortable to wear.

Conclusions These 12-month results are consistent with previously reported 6-month outcomes from this study, showing durability of peripheral nerve stimulation treatment with the micro-IPG system; subjects realized sustained large reduction in pain and improvement in patient-reported outcomes following treatment with this micro-IPG system.

Trial registration number NCT05287373.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Peripheral nerve stimulation (PNS) is a well-established effective therapy for treating chronic pain of peripheral nerve origin. It has been widely used for over 50 years around the globe.

⇒ However, there is a paucity of data from randomized clinical trials, especially with long-term follow-up. The 6-month published results from the current randomized controlled trial demonstrated early favorable outcomes.

WHAT THIS STUDY ADDS

⇒ This study showed that PNS therapy delivered by a micro-implantable pulse generator (IPG) continues to provide statistically significant improvement in pain, disability, mood and quality of life out to 12 months.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The outcomes of this study provide a basis for long-term clinical evidence to support patient access to appropriate PNS therapy, as delivered by the micro-IPG.

⇒ The results reported here further enhance clinical confidence in the application of PNS therapy for appropriate patients.

INTRODUCTION

Peripheral nerve stimulation (PNS) is a well-established modality for the treatment of chronic pain (CP) of peripheral nerve origin. It was first used clinically in the 1960s[1] and has been the subject of multiple clinical studies.[2] The prevalence of neuropathic pain may be as high as 10% in the general population.[3] Traditionally, PNS has been prescribed only after other therapies have failed (eg, physical therapy, nerve blocks, over-the-counter pain medications, and opioids).

PNS therapy requires a successful trial phase and the permanent implant of an implantable pulse generator (IPG) and electrodes. To qualify for a permanent implant, patients are generally required to achieve ≥50% pain reduction during the trial phase. For the permanent implant, electrodes are implanted in close proximity to the targeted nerve(s), a pocket

for the IPG is created and the electrodes are connected to the IPG. In the USA, PNS devices are assigned a specific product code (GZF, Stimulator, Peripheral Nerve, Implanted (Pain Relief)) by the US Food and Drug Administration (FDA) and are designated for implantation. This differentiates PNS devices from devices without a permanent option, such as percutaneous electrical nerve stimulation or transcutaneous electrical nerve stimulation devices. These devices are assigned different FDA-product codes (eg, NHI) and are not designated as implanted devices.

This study was undertaken, in part, to provide randomized controlled trial (RCT) results to support continued patient access to appropriate PNS therapy. We previously reported 3-month and 6-month results from this study,[4] and we now report 12-month results, including the entire evaluable population. The results are from the first large, postmarket, multicenter, on-label, 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-IPG.

The micro-IPG system (Nalu Neurostimulation System, Carlsbad, California, USA) used in this RCT has FDA 510k clearance for both PNS and spinal cord stimulation (K183579, K191435). The micro-IPG is battery-free with a volume of $<1.5\,cm^3$, and a cleared service life of 18 years. The system is powered by a small, externally worn battery (therapy disc (TD)), which allows software updating without replacing the implanted components. Like other FDA-designated PNS systems, the micro-IPG system allows for a temporary trial phase. This device offers advanced programming options and waveforms comparable to the most sophisticated fully implantable IPGs (see Kalia *et al*[5] 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 designed with input from physician experts in PNS and from representatives of US insurance payers. The intent of including such input was to ensure that the data addressed concerns related to coverage for appropriate PNS therapy.

The study was conducted at 12 pain management centers in the USA, which included a range of academic and private-practice centers. Enrolment took place between February 23, 2022 and March 29, 2023. Following completion of the IRB-approved informed consent process, subjects were screened for eligibility. Briefly, subjects were required to be between 18 and 80 years of age and have the following: a diagnosis of CP of peripheral nerve origin (chronic was defined as at least 6 months) in the low back, shoulder, knee, or foot/ankle. Pain etiology was post-surgical/post-traumatic peripheral neuralgia including pain due to peripheral nerve injury. The protocol was updated to include postsurgical scar formation, nerve entrapment, mononeuropathy and osteoarthritic pain. This was to better align eligibility with the real-world clinical environment and the standard of care for PNS. Subjects were excluded if they had one or more of the following: complex regional pain syndrome, peripheral neuralgia of metabolic origin, postherpetic neuralgia, on ≥90 mg morphine equivalents per 24 hours, failure to pass psychological evaluation, and/or inability to wear or use the micro-IPG system. Complete eligibility criteria are listed on the ClinicalTrials.gov website and Hatheway *et al*.[4]

Those who met study eligibility criteria were randomized to either the active arm or control arm. Subjects randomized to the active arm received PNS and CMM, while subjects randomized to the control arm received CMM alone (figure 1). Randomization details are described in Hatheway *et al*.[6] Subjects randomized to the control arm continued to receive their prescribed CMM alone for 3 months. Details of CMM were outlined in Hatheway *et al*.[6] At the 3-month time point, control arm subjects were given the option to crossover into the active arm. Following crossover, subjects followed the same schedule and

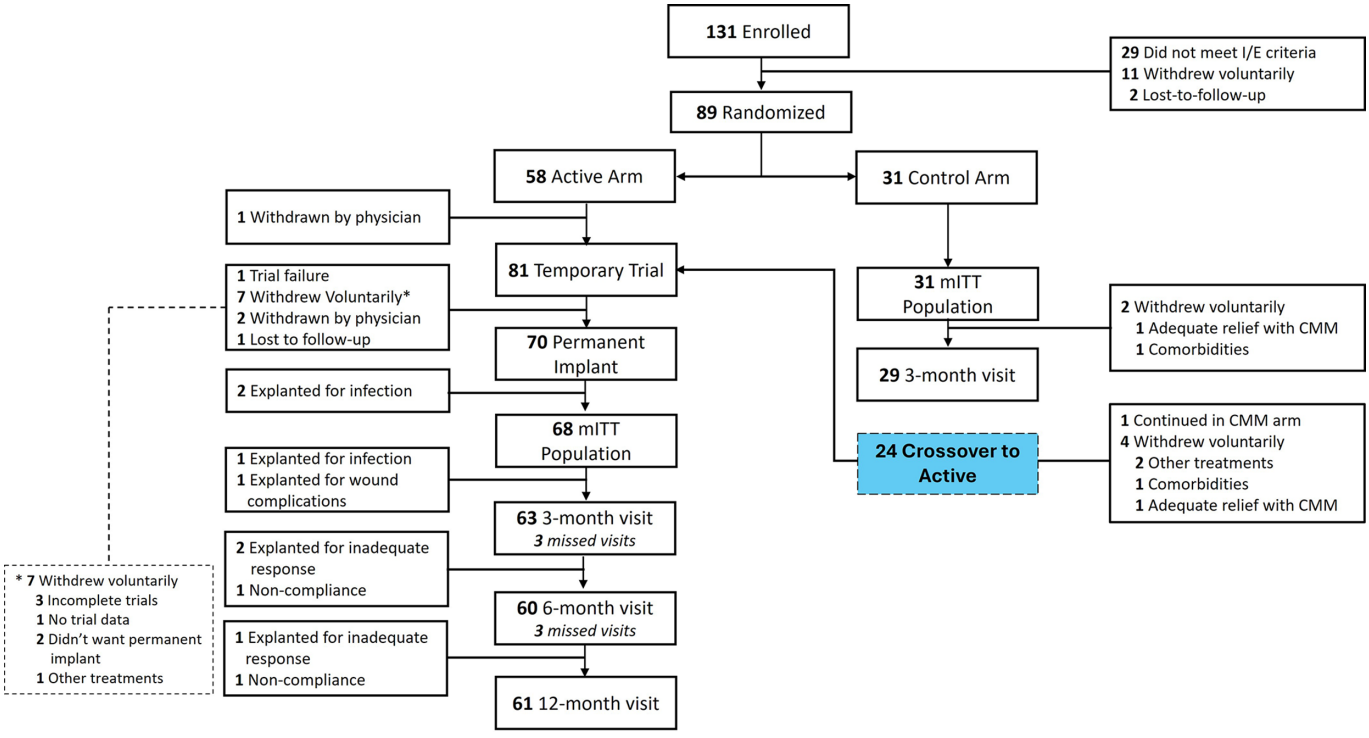


Figure 1 Subject disposition from consent to 12-month follow-up with initial group assignment and crossover from control arm to active arm. Subjects who had missed visits were included at next visit. CMM, conventional medical management; mITT, modified intention to treat.

study procedures as those originally assigned to the active arm beginning with a temporary trial lead placement.

Subjects in the active arm continued to receive CMM with the addition of PNS therapy per the standard of care and following the device labeling. There were no experimental devices or procedures as part of this study. This standard of care included a temporary trial procedure during which each subject was required to achieve ≥50% reduction in pain (defined as a "responder") to be eligible for a permanent implant. Those who were responders continued to the implant phase at which time they received a permanent implant of the micro-IPG and permanent lead(s). Those who were not responders were considered screen failures and exited the study.

Following adequate healing time, the device was programmed to optimal patient effect using paresthesia-based and/or paresthesia-independent programs. All programming was on-label and was performed following the usual standard of care by trained industry clinical specialists under the direction of a study physician. The micro-IPG system uses complex programming, similar to the capabilities of SCS systems[7] (pulse widths of ≥500 µs, frequencies ≥500 Hz, use of more than 2 electrodes, multiarea, cross-lead, current steering, and/or proprietary waveforms). Programming data on were available for 57 of the 61 subjects, which showed approximately 65% of subjects in the study used pulse widths ≥500 µs and frequencies ≥500 Hz, whereas 70% used >2 electrodes (anodes/cathodes combinations). A majority of programs (77%) were multi-area with about 30% of subjects preferring a scheduled program (rotating through multiple programs). Subjects were given a choice of up to 8, subparesthesia and supraparesthesia, stimulation programs, which they could cycle through based on the therapeutic benefit. Clinical equipoise was maintained by both arms being treated equally, except for the implant procedures.

Subjects were followed at 1, 3, 6, 9, and 12 months to collect the patient-reported outcomes (PROs) and safety data. Subjects will be followed out to 36 months. This report focuses on the 12-month results as the study is ongoing. Patient safety was ensured by tracking adverse events (AE), serious adverse device effects (ADEs) and serious AEs (SAEs) over the course of the study. Numeric Rating Scale (NRS) pain score, from the target area of peripheral pain, was the primary efficacy outcome measure, and it was captured with the Brief Pain Inventory (question 5; BPI-Q5). Additional PROs were as follows: Patient Global Impression of Change (PGIC), BPI Short Form (BPI SF), Quality-of-Life metric (EuroQol-5 Dimensions-5 Level, EQ-5D-5L), Beck Depression Inventory (BDI), Oswestry Disability Index (ODI). Device comfort and usability were captured in addition to subject satisfaction and compliance with the therapy.

Statistical analysis

Primary endpoint analysis was carried out on the modified-intention-to-treat (mITT) population, as prespecified in the statistical analysis plan. The mITT population was defined as "all randomized subjects receiving a permanent implant and having an implant at the time of analysis in the active arm and all randomized 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. This primary-endpoint analysis was published

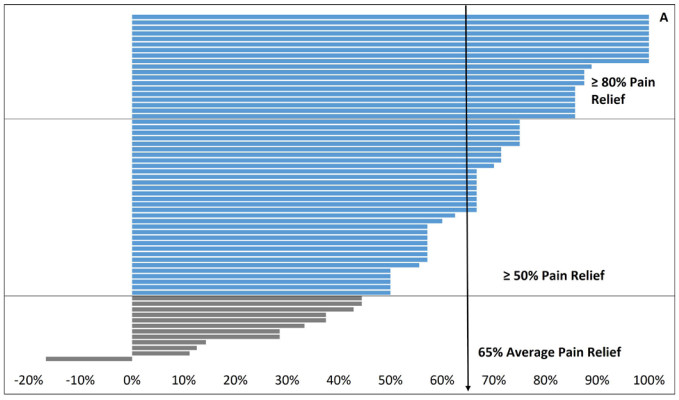


Figure 2A. Individual subject pain relief at 3-months for subjects in the combined cohort (n=63)

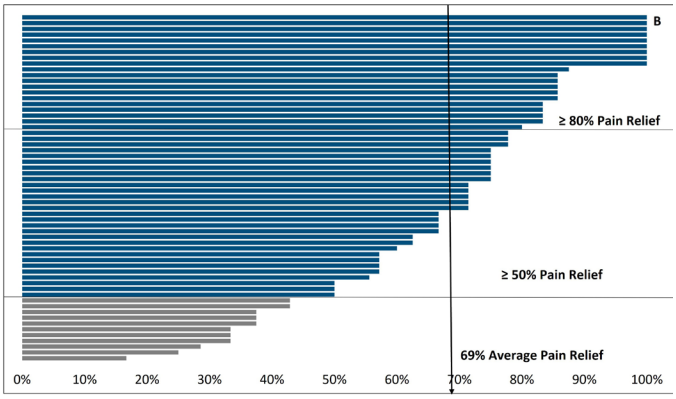


Figure 2B. Individual subject pain relief at 6-months for subjects in the combined cohort (n=60)

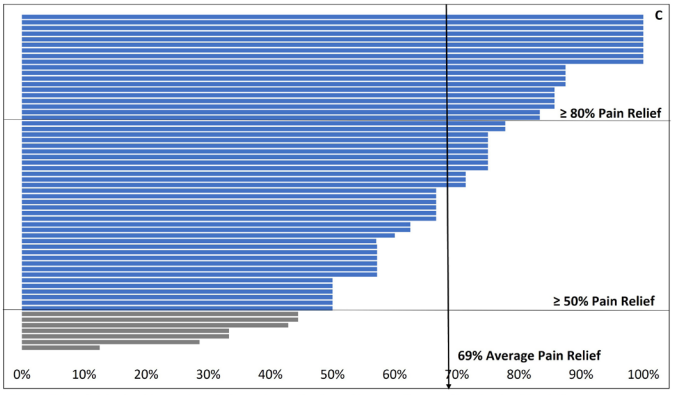


Figure 2C. Individual subject pain relief at 12-months for subjects in the combined cohort (n=61)

Figure 2 Tornado plot (A) (combined cohort at 3 months), (B) (combined cohort at 6 months) and (C) (combined cohort at 12 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.

in Hatheway *et al*.[4] The calculated sample size for the study was 87 and was based on power requirements for the primary effectiveness endpoint. Missing data are assumed to be missing completely at random. Results were reported as mean±SD for continuous variables and as percentage (count) for categorical variables, unless otherwise noted. Comparisons between baseline and follow-up were conducted by two-sample t-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.

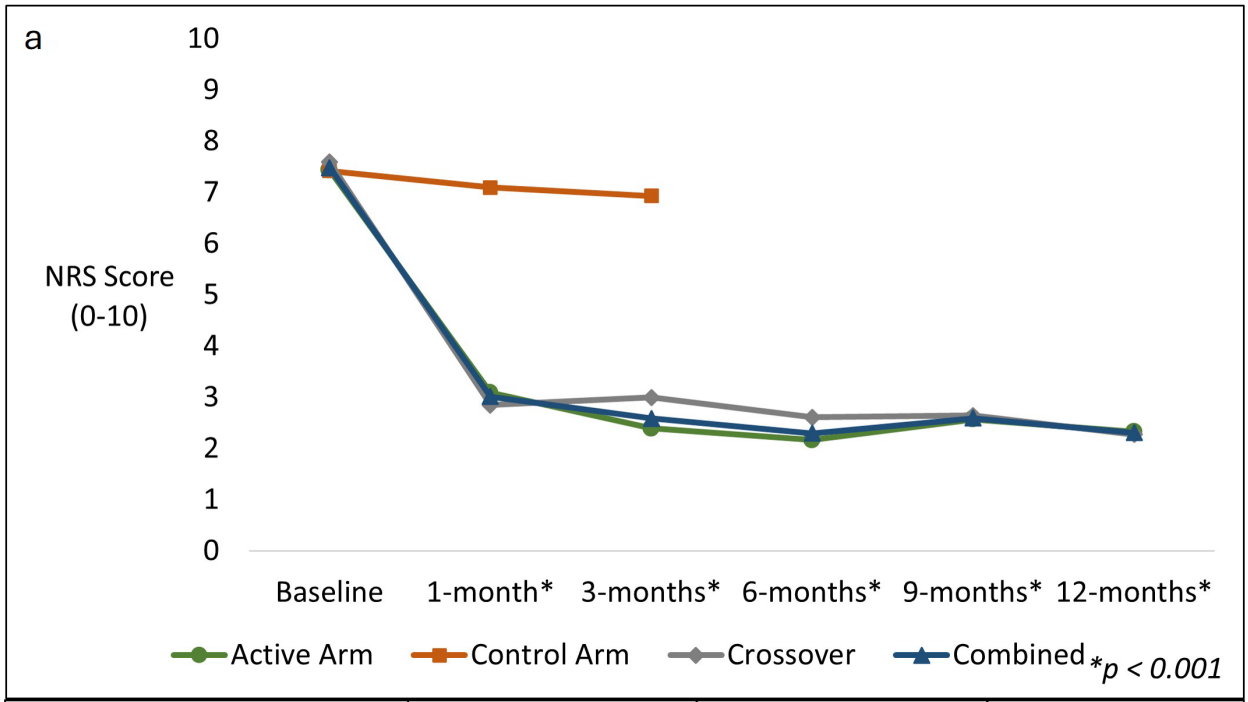
RESULTS

Of the 131 subjects who were consented, 58 were randomized to the active arm and 31 to the control arm. 24 subjects in the control arm met the criteria to crossover to the active arm and receive PNS therapy. A detailed subject disposition is shown in figure 1. For details on the demographics and medication usage please refer to Hatheway *et al*.[4] The distribution across the anatomic areas of pain was 49.4% low back, 20.8% in the knee, 16.9% in the foot/ankle and 13% in the shoulder. The targeted nerves are listed in Hatheway *et al*.[4]

For all subjects at 12 months, the responder rate was 87% (53/61) with an average pain reduction of 69% (figure 2C). Mean pain scores (NRS) improved from 7.5±1.20 at baseline to 2.3±1.7 at 12 months. This was consistent throughout the duration of the study, to date (figure 3). For the cross-over subjects, at 12 months, the responder rate was 89% (16/18) with an average pain reduction of 69%. Mean pain scores improved from 7.6±1.2 at baseline to 2.3±2.2 at 12 months. For those originally randomized to the active arm at 12 months, the responder rate was 86% (37/43) with an average pain reduction of 68%. Mean pain scores improved from 7.4±1.2 at baseline to 2.3±1.5 at 12 months. Figure 3 shows consistency among the three cohorts (combined, crossover, active). 31% (19/61) of subjects were high responders, with ≥80% pain improvement from baseline in the combined cohort; this was 39% (7/18) and 28% (12/43) in the crossover and active cohorts, respectively (figure 2).

The average pain reduction was consistent across the four anatomic areas in the study with a 66% improvement in the low back, and 72% in the knee and shoulder and 71% in the foot/ankle.

Similar alignment of outcomes between the cohorts was seen for the secondary endpoints as well. Table 1 shows the outcomes for BPI-SF (both interference and severity), Quality-of-Life metric (EQ-5D-5L), BDI, ODI. Note that all comparisons



b	Combined Arm		Active Arm		Crossover Arm	
Timepoint (in months)	6	12	6	12	6	12
Responder Rate	82%	87%	88%	86%	67%	89%
% Mean Relief	69%	69%	70%	68%	65%	69%
p-value	p < 0.001		p < 0.001		p < 0.001	

Figure 3 Mean NRS pain scores (BPI-Q5) and responder rates from baseline to 12 months. (a) Pain scores captured in the office at baseline, and at 1 month, 3 months, 6 months, 9 months and 12 months, for the combined, the crossover cohorts and the original active and control arms. Mean per cent reduction in pain was statistically significant in the combined, crossover and active cohorts at each time point (p<0.001). Each data point represents the mean. Error bars were omitted for clarity; SD is listed in the Results section. (b) Responder rates (≥50% improvement) and per cent pain reduction at 6 and 12 months. Pain relief in each cohort was significantly better than baseline (p<0.001). BPI-Q5, Brief Pain Inventory question 5; NRS, Numeric Rating Scale.

Table 1 Patient-reported outcomes

	Combined arm		Active arm		Crossover arm	
Assessment	**Baseline**	**12 months**	**Baseline**	**12 months**	**Baseline**	**12 months**
	Mean±SD (N)	Mean±SD (N) (mean % change)	Mean±SD (N)	Mean±SD (N) (mean % change)	Mean±SD (N)	Mean±SD (N) (mean % change)
BPI-severity	6.82±1.58 (68)	2.90±1.93 (59) (55; p<0.001)	6.69±1.51 (46)	2.84±1.73 (42) (56; p<0.001)	7.10±1.71 (22)	3.04±2.40 (17) (53; p<0.001)
BPI- interference	6.21±2.00 (68)	2.43±2.16 (59) (55; p<0.001)	5.99±2.16 (46)	2.19±2.00 (42) (55; p<0.001)	6.69±1.55 (22)	3.04±2.46 (17) (55; p<0.001)
BDI	12.9±9.96 (68)	5.97±6.84 (61) (35; p<0.001)	11.87±9.48 (46)	5.84±6.45 (43) (33; p=0.001)	15.05±10.8 (22)	6.28±7.89 (18) (39; p<0.05)
EQ-5D-5L	0.603±0.15 (68)	0.815±0.13 (61) (49; p<0.001)	0.629±0.16 (46)	0.812±0.13 (43) (46; p<0.001)	0.549±0.11 (22)	0.821±0.13 (18) (57; p<0.001)
ODI	44.93±13.66 (68)	22.84±16.93 (60) (45; p<0.001)	42.78±13.3 (46)	21.88±14.9 (42) (43; p<0.001)	49.42±13.32 (22)	25.07±21.28 (18) (51; p<0.001)
ODI categorical	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)
Minimal	3 (2)	48 (29)	2 (1)	52 (22)	5 (1)	39 (7)
Moderate	40 (27)	37 (22)	50 (23)	36 (15)	18 (4)	39 (7)
Severe	44 (30)	12 (7)	37 (17)	10 (4)	59 (13)	16 (3)
Crippled	13 (9)	3 (2)	11 (5)	2 (1)	18 (4)	6 (1)
Bed bound	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

BDI, Beck Depression Inventory; BPI, Brief Pain Inventory; EQ-5D-5L, EuroQol-5 Dimensions-5 Level; ODI, Oswestry Disability Index.

between baseline and 12 months outcomes were statistically significant.

All three cohorts met the minimal clinically important difference (MCID) for PGIC (minimally improved, much improved or very much improved). For all subjects, 48% (29/61) reported very much improved, 44% (27/61) reported much improved, 3% (2/61) reported minimally improved, 5% (3/61) reported no change and none of the subjects reported minimally worse, much worse, and very much worse (figure 4B). For the cross-over subjects, 89% (16/18) of subjects reported improvement with 11% (2/18) of subjects reporting no change. For those originally in the active arm, 98% (42/43) reported improvement with 2% (1/43) reporting no change.

All subjects rated their overall satisfaction with the micro-IPG system using a 5-point Likert scale. 92% (56/61) of all subjects were either very satisfied (74%; 45/61) or satisfied (18%; (11/61) with the system; 3% (2/61) were neutral and 5% (3/61) were dissatisfied with the system. Subjects also reported their ratings for the comfort of wearing or using the device. 80% (49/61) reported that the wearable was very comfortable or comfortable and 92% (56/61) reported the device to be very easy or easy to use. 87% (53/61) reported using the device for at least 10 hours/day with 72% (38/53) of them reporting device use for a full day.

Subjects continued CMM regimen as needed. At 12 months, 93% (57/61) of subjects reported continued use of oral medications and 20% (12/61) using topical applications for pain. Other CMM reported include physical therapy (2), psychological therapy (4), nerve block (1), epidural steroid injection (1), bracing (9), ice/heat (3) and toradol injection (1). To note, the protocol required subjects to keep pain medications stable through the study.

The study maintains an excellent safety record with no unanticipated serious ADEs or SAEs related to the device or procedure having been reported. Nor were there any reports of pocket pain. All non-serious ADEs were resolved with no sequelae. At the 12-month time point, lead and/or micro-IPG migration was reported in 10 patients, which resulted in revision procedures to reposition the micro-IPG and/or correct lead position. Three instances of lead fracture were reported which resulted in lead replacement. One patient had a mild infection

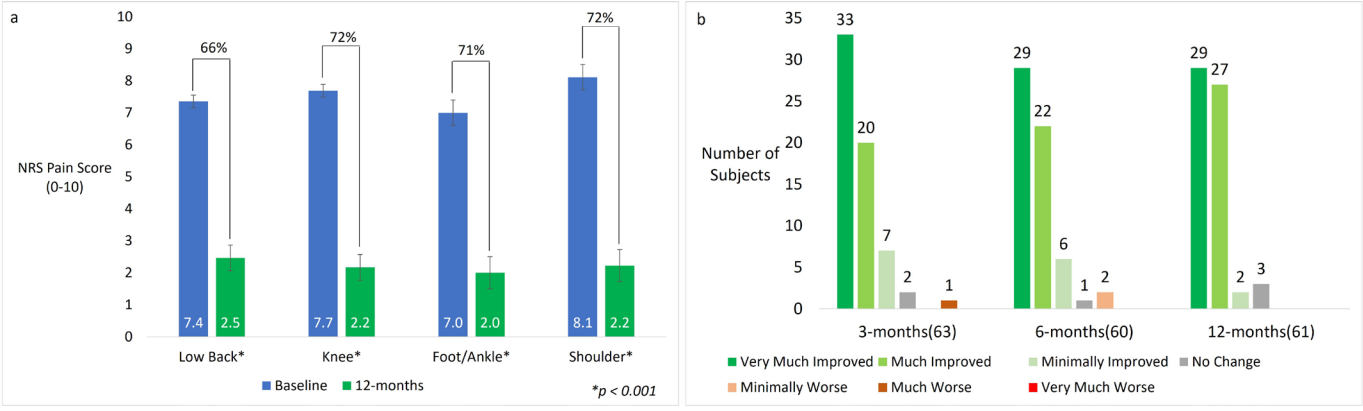


Figure 4 (a) Pain relief by area of pain with mean per cent pain relief from baseline to 12 months. The improvement in pain was statistically significant in each of the four areas of pain at 12 months, when compared with baseline. (b) Patient Global Impression of change at 3, 6 and 12 months. 95% of subjects reported improvement with PNS therapy at 12 months. NRS, Numeric Rating Scale; PNS, peripheral nerve stimulation.

at the implant site that resolved without sequelae, following treatment with antibiotics (oral cephalexin 500 mg, four times a day for 15 days). Three other patients had infections post-implant; had their devices explanted, the infections resolved and the subjects discontinued study participation. One subject had wound complications which required medical intervention with device explant. 10 non-device, non-procedure-related SAEs were reported in the combined cohort, all resolving with no sequelae.

DISCUSSION

The results presented here are long-term outcomes from the first RCT examining the treatment of peripheral neuralgia/neuropathy with an externally powered micro-IPG, where CMM+PNS outcomes were compared with CMM alone. Responder rates ranged from 86% to 89% at 12 months, depending on which of the cohorts (active, crossover, combined) were considered. Pain reduction was 69% across all three cohorts. In addition, all PROs were statistically superior at 12 months, compared with baseline. In the case of device satisfaction, comfort and ease of use, the score was high on a 5-point Likert scale.

It is noteworthy that there is only one other RCT looking at the treatment of peripheral neuropathy/neuralgia with PNS[8]; StimRouter, Bioventus,), the outcomes of which were less powerful than the current study. For example, 38% in the active arm vs 10% in the control arm were responders based on a responder rate criterion of 30%, rather than the 50% criterion used in this study (which is now more common). When the COMFORT results were analyzed using the 30% responder rate criterion, the COMFORT responder rate improved to 95% (41/43) in the active arm and to 10% (3/29) in the control arm.[4] The pain relief in the Deer *et al* study[8] was 27% for the active arm vs 2.3% pain reduction in the control arm at 3 months, whereas the pain reduction at 12 months was 69% in the COMFORT study.

The weaker outcomes in the previous Deer study as compared with the current COMFORT study may arise from improvements in technology in the intervening years. Unlike the earlier generation of PNS devices, the micro-IPG has similar functionality to the most advanced SCS IPGs, which includes the following features: up to 16 electrode contacts, complex programming (multicontact >2), multiarea, high pulse width (>500 µs), high frequency (>500 Hz), multiprogram scheduling, cross-lead current steering and a proprietary (Pulsed-Stimulation Pattern) waveform. In fact, analysis of programming in this study found that high pulse widths and frequencies were used about 65% of the time, and >2 electrodes were used 70% of the time, and 77% of programs were multi-area.

In the current study, the 7–10 days trial responder rate of 93% (75/81; 50% responder rate criterion) shows that a longer trial period is not needed to identify appropriate patients. False positives are also not an issue in the current study, as the 12-month responder rate was 87%.

It is interesting that after 12 months of use, 92% of subjects were satisfied with the system and found it easy to use, while 80% found it to be very comfortable or comfortable. This is consistent with earlier studies with the same device treating low-back and leg pain with SCS.[9 10] This may, in part, be due to the fact that patients have the option of using a cuff or adhesive clip to hold the TD in place over the IPG. For example, the use of a cuff on a limb may be more comfortable than a clip. In addition, the patients are given the opportunity to choose the best location during a wear assessment. This then allows the patient and implanting physician to agree on the best micro-IPG placement. In addition, the lack of micro-IPG pocket pain[11 12] was also sure to contribute to these favorable comfort ratings.

PROs beyond NRS pain scores included BDI, BPI, ODI, EQ-5D-5L. All of these outcomes were statistically superior to baseline scores. The majority of the subjects achieved MCID at 12 months for the various PROs (PGIC-95%, ODI-73%, BDI-78%, BPI-Interference-83%, EQ-5D-5L- 70%), which assesses overall improvements in a clinically meaningful way rather than relying only on pain scores. The outcomes indicate that treatment with the micro-IPG provides a robust therapeutic response.

Limitations

Limitations of this study include the fact that this is not a double-blind study, which can increase the risk of expectation bias (blinding was considered during the initial design phase but not executable given the nature of the device and its programming capabilities). Also, the control arm was in CMM for 3 months. However, requiring patients to remain in severe pain when it was known that CMM was not effective in the preceding years prior to the study was problematic, especially when earlier studies pointed to a high likelihood of relief from PNS. Hence, a longer CMM arm was thought to violate the bioethical standard of beneficence.[13 14] In addition, the study did not use a questionnaire to assess neuropathic pain but instead relied on best clinical practice. These instruments are not routinely used in the USA, are not required by US healthcare policy and did not conform to the pragmatic design of the study. Also not all CMM options were available to subjects and were dependent on factors such as physician prescribing practices, patient preference, availability and access to treatment, and importantly, insurance coverage of prescribed CMM; this reflects the usual CMM care patients receive in the US outside of any study and was not the focus of the study. However, even with these limitations, this study represents a significant advancement in the PNS field. The study is one of the very few RCTs in PNS involving permanent implants and is the only PNS RCT involving the current generation of advanced programming-capable PNS devices.

CONCLUSIONS

This study demonstrated that PNS therapy delivered by a micro-IPG using advanced programming provided robust and consistent, statistically significant improvement in pain, disability, quality of life, and mood. This level of long-term (12 months) improvement from PNS across a spectrum of anatomic areas has not been previously reported. The strong safety profile, including no reports of pocket pain, SADE or SAEs related to the device, has been consistent throughout the course of the study. The strong patient satisfaction and comfort scores provide confidence that device usage will be maintained. The small size of the micro-IPG (<1.5 cm^3) allowed it to be optimally placed for each patient without form-factor constraints. The study is ongoing, and the authors will report additional results as they become available.

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