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Randomized Controlled Trial

A Prospective, Randomized, Controlled Clinical Trial of High-Frequency Electromagnetic Coupling Powered Permanent Peripheral Nerve Stimulator for the Treatment of Chronic Craniofacial Pain

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Background: Craniofacial pain is one of the most common chronic pain conditions, affecting more than one-fifth of the US population. While various medications and conservative treatment modalities are available for this condition, many patients have refractory symptoms. These patients suffer from social impairment, reduced quality of life, and increased financial burdens.

Objective: The objective of this study was to examine the clinical outcomes of patients receiving a permanent, high-frequency electromagnetic coupling (HF-EMC) powered peripheral nerve stimulator (PNS) system for the treatment of chronic craniofacial neuropathic pain.

Study Design: This study was a multicenter, randomized, controlled clinical trial conducted under an investigational device exemption (IDE).

Setting: This study was conducted in 7 clinical sites in the US.

Methods: All patients in this randomized controlled trial (RCT) were permanently implanted with the Freedom® Peripheral Nerve Stimulator (PNS) System (Curonix LLC). All patients completed an initial 7-day therapy assessment period following the permanent implantation. The patients who successfully completed the initial 7-day therapy assessment period (≥ 50% pain relief) were randomly assigned to either a patient group that received continued stimulation (the "active" arm) or a patient group whose treatment was discontinued for 3 months after the initial positive 7-day therapy assessment period (the "deactivated" stimulation arm). After the 3-month follow-up visit, the deactivated patients were reactivated. The primary efficacy outcome included the proportion of patients who experienced significant pain relief (≥ 50%) 3 months after the permanent implant procedure. The visual analog scale (VAS), Brief Pain Inventory Facial (BPIF) questionnaire, and Short-Form McGill Pain Questionnaire 2 (MPQ-SF-2) were used to measure changes in pain. Additional functional outcome measures included the Patient Global Impression of Change (PGIC) and the 36-Item Short-Form Survey (SF-36).

Results: During the 7-day therapy assessment period, 56 out of 60 patients reported significant pain relief (≥ 50%), representing a 93% responder rate. At 3 months, 69% of the active stimulation group experienced significant pain relief, while only 11% of the deactivated group reported significant pain relief. The mean VAS scores were reduced by 62% and 8.5% in the active and deactivated stimulation groups. When patients within the deactivated group were reactivated after 3 months, the reactivated patients reported similar reduction in pain scores to those reported by the active arm patients. Similar results were found for the functional outcome measures. After the reactivation, significant pain relief was maintained through the 12-month follow-up period. No SAEs were reported throughout the study for any of the patients.

Limitations: Limitations include the lack of true placebo due to the required use or nonuse of the external transmitter as control per the study design, the optional utilization of supra- or sub-threshold stimulation, and variations in patient follow-up due to the COVID-19 pandemic.

Conclusion: This RCT operated under an IDE requiring regulatory FDA oversight. This study provides Level 1 evidence for PNS therapy. The positive outcomes of this study support an expanded PNS indication for the treatment of craniofacial pain. The study confirms that HF-EMC powered permanent PNS is an effective and safe intervention for refractory chronic craniofacial neuropathic pain.

Key words: HF-EMC powered permanent peripheral nerve stimulator (PNS), peripheral nerve stimulation (PNS), peripheral nerve stimulation interventional techniques, peripheral neuropathic pain, chronic pain, chronic craniofacial pain, occipital nerve, trigeminal nerve, craniofacial peripheral nerve stimulation (CFPNS)

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Stimulation of the peripheral nerves is a broad therapy category that includes various modalities such as permanent peripheral nerve stimulation (PNS), peripheral nerve field stimulation (PNFS), percutaneous electrical nerve stimulation (PENS), and transcutaneous electrical nerve stimulation (TENS). To distinguish these different modalities from one another, the FDA classifies the product under a Product Code unique to each modality. Understanding the key differences in stimulation treatments is critical. Each FDA-cleared PNS product classification is associated with different indications for use, different mechanisms of action, and varied levels of evidence (Table 1). The work, knowledge, and surgical and interventional skillset requisite for permanent PNS implants exist in a completely different category from the other procedures discussed (1). PNS is placed directly near a named, targeted nerve identified as the cause of chronic pain.

Physicians have utilized PNS therapy since the 1960s (2). Today, many long-term peer-reviewed studies exist investigating the outcomes of the 2-component receiver-based PNS system in various nerve targets. Helm and colleagues conducted a systematic review to assess the status of high-quality evidence supporting the use of PNS in treating chronic pain conditions of peripheral nerve origin. The evidence suggests that approximately two-thirds of patients with peripheral neuropathic pain will experience sustained pain relief of at least 50% with PNS (3). In 2024, the American Society of Interventional Pain Physicians (ASIPP) published evidence-based guidelines supporting the use of implantable PNS systems in patients with moderate to severe chronic pain refractory to conservative treatments. These robust guidelines provide a comprehensive review and critical analysis regarding the growing evidence supporting the use and long-term efficacy of PNS in clinical practice (4). The guidelines included 4 Freedom® PNS studies, representing 213 patients, in which the guideline authors concluded that the data appeared to provide reliable and reproducible evidence for successful PNS treatment. In addition to the ASIPP PNS guidelines, the Freedom® PNS system has been researched extensively in over 340 patients with various nerve targets, including the upper and lower extremities and craniofacial nerves, as established in this study.

It is important to note that efficacy and safety results have been demonstrated consistently in multidisciplinary environments, as highlighted here in recent Freedom PNS publications. Multiple data sets exist describing the treatment of chronic pain in interventional pain practices. For example, Abd-Elsayed and Moghim reported a mean of long-term pain improvement of over 70% in a total of 57 patients with various neuralgias (5). Patients also reported a significant reduction in the doses of morphine milliequivalents they consumed. Similar outcomes were reported in retrospective reviews for the treatment of chronic pain in various locations. Pollina investigated the effects of PNS for the treatment of chronic foot pain (n = 15); the patients in that study indicated a long-term mean reduction of 65% (6). Lindley focused on the treatment of patients (n = 21) with lower back pain by targeting the superior cluneal nerve and described long-term pain reductions of 57% (7). Wiederholz targeted the brachial plexus for the treatment of chronic shoulder pain (n = 7) and witnessed pain reductions of up to 83% (8). Früh and Bayerl focused on the treatment of knee pain in a neurosurgical practice (n = 33) and showed up to 75% pain relief, with reductions in pain medication usage (9). The orthopedic literature further confirms similar results. Mates reported decreased pain scores with a mean of 73% 3 months after permanent implant in a population treated for chronic pain in the lower and upper extremities (10). Kilbride reported similar results

for the treatment of chronic knee pain in 7 patients, with 87% mean pain reduction (11). The patients who were followed in those studies consistently reported significant long-term pain reduction, improved quality of sleep, reduced pain medication usage, and high satisfaction rates. Furthermore, out of 175 patients, only 9 complications (5%) were reported in this body of evidence, with one isolated serious adverse event (Table 2).

The total body of PNS clinical evidence consistently supports the efficacy and safety of this modality for chronic pain relief (3-11). As such, in the United States, Medicare beneficiaries have had access to PNS through a long-standing national coverage determination (NCD) providing coverage of PNS indications with evidence of efficacy since 1995 (12). In addition to the NCD, a large Medicare Administrative Contractor published a local coverage determination (LCD) providing coverage guidance for PNS (13).

Craniofacial Pain: The etiologies for craniofacial pain are complex and may be related to the extensive innervation of the head and face (14). In addition to causing patients physical discomfort, craniofacial pain can bring social impairment, reduced quality of life, and increased financial burdens (15). The International Classification of Headache Disorders (ICHD) has established that the general categories of craniofacial pain are primary headaches, secondary headaches, and a category that includes painful cranial neuropathies, other facial pains and other headaches (16).

Conventional management of craniofacial pain varies depending on the etiology. The management of painful cranial neuropathies involves primarily pharmacological therapies. These include but are not limited to opioids, anticonvulsants, tricyclic antidepressants, and topical agents. Common nonpharmacological treatment options for craniofacial pain include cognitive behavioral therapy, stress management, relaxation techniques, biofeedback, and the improvement of sleep hygiene. Current treatment strategies are often temporary and may not adequately manage patients' symptoms.

Nerve injections have traditionally been utilized to target and temporarily treat chronic pain of peripheral nerve origin. Historically, nerve ablations have been used to manage craniofacial pain disorders such as occipital neuralgia; however, the ensuing pain relief is usually short-lived (17). A more permanent treatment modality for craniofacial pain may include a 2-component, receiver-based PNS system (18). PNS is an intervention in which electrode arrays are placed at the targeted peripheral nerves identified as the origin of pain (19) and then connected to a separate receiver.

The present randomized controlled trial (RCT) included patients with craniofacial pain who underwent permanent implantation of a peripheral nerve stimulator. Patients were randomized into 2 categories, active PNS or deactivated PNS, for the purpose of comparing the modalities' safety and efficacy outcomes using a high-frequency electromagnetic coupling (HF-EMC) powered device targeting craniofacial nerves.

Table 1. *Examples of different nerve stimulators and associated FDA clearance.*

Procedure	PNS	PNFS	PENS	TENS
Description	Peripheral nerve stimulation	Peripheral nerve field stimulation	Percutaneous electrical nerve stimulation	Transcutaneous electrical nerve stimulation
FDA product code*	GZF	PZR	NHI	GXY, NUH, NGX

*Sourced by FDA Classification Product Code.

Table 2. *Examples of published evidence.*

	Study Sample	Pain Location	Pain Reduction	Non-Serious AE's	SAE's
Abd-Elsayed	57	Various	81%	3	0
Pollina	15	Foot	65%	1	0
Lindley	21	Low back	57%	0	0
Wiederholz	7	Shoulder	83%	0	1
Früh	33	Knee	75%	2	0
Mates	14	Various	73%	2	0
Kilbride	7	Knee	87%	0	0

Methods

Device Description

The PNS system used in this study (Freedom® PNS System by Curonix LLC, Pompano Beach, FL) includes an implanted electrode array (with 4 or 8 contacts) (Fig. 1), a separate implanted receiver, and an external transmitter assembly and wearable accessory (Fig. 2). The external transmitter uses HF-EMC technology to transfer data and stimulation energy wirelessly to the 2-component implant that the physician connects during the procedure. The physician is also required to create a separate, distinct pocket to anchor the device permanently.

Study Design

This study was a multicenter, randomized, controlled clinical trial conducted under an investigational device exemption (IDE) intended to support FDA clearance through a 510(k) for the extension of the existing indication to include treatment in the craniofacial region for chronic neuropathic pain (ClinicalTrials.gov NCT02729480; FDA 510(k) K233162). The objective of this study was to assess the safety and efficacy of permanent PNS therapy with a neurostimulation system to treat chronic pain in the craniofacial region, refractory to standard medical treatment.

Patient Selection

The study population consisted of patients who were diagnosed with craniofacial neuropathic pain refractory to standard medical treatment and who met all the selection criteria but none of the exclusion criteria (Appendix 1). The site investigators recruited potential patients from the clinics' patient population, and patients were included in the study once they had signed an informed consent form.

The study was conducted at 7 sites (Table 3) in the USA after being granted an IDE by the FDA, since the PNS system was not yet cleared for use in the craniofacial region prior to the study. After approval by the corresponding investigational review boards (IRBs), 85 patients were screened, and of those patients, 60 who had chronic neuropathic pain in the craniofacial region were deemed eligible. Those patients were recruited into the study between March 2017 and February 2021. After giving informed consent, patients were block randomized at a one-to-one ratio and assigned to either an active (continued stimulation) or a deactivated (temporarily without stimulation) group. The randomization assignments were sent to each site in numbered, sealed opaque envelopes. A representative from the site opened the sealed envelopes and assigned the patients to either group during the preoperative baseline visit. All patients received a permanently implanted peripheral nerve stimulator system at the targeted nerve in the painful craniofacial region without a prior temporary trial implant. Target nerves were restricted to branches of the trigeminal and occipital nerves. Devices for all patients were then activated postoperatively, with parameter settings established based on sensory response and patients' comfort levels. Patients were seen after a 7-day therapy assessment period for compliance and clinical response. The patients who did not respond to the therapy with at least a 50% reduction in their pain levels were deemed non-responders, withdrawn from the study, and received the option to have the permanent device removed.

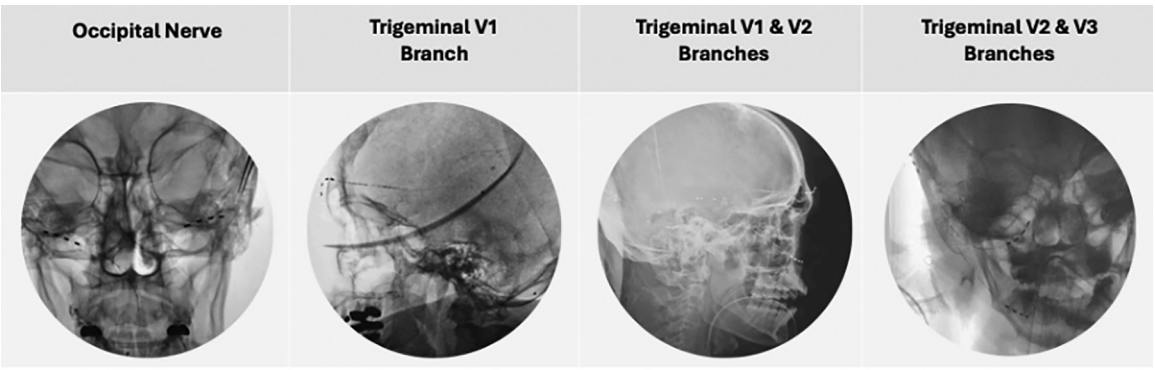

Fig. 1. *The x-rays provide examples of the 2-component neurostimulator (electrode array and separate receiver) implantation for the occipital nerve and trigeminal nerve branches.*

Afterward, patients who responded during the initial 7-day therapy assessment period were then randomized to receive either peripheral nerve stimulation (active arm) or no stimulation (deactivated arm) for the next 3 months. The assignment was achieved by the utilization or absence of utilization of the external transmitter. As such, neither patients nor assessors were blinded to the assignment. Patients in both groups followed their study assignment for 3 months after the initial 7-day assessment period. Three months later, the active-arm patients continued with stimulation for an additional 9 months. The deactivated-arm patients had the opportunity to resume active stimulation treatment and continued with therapeutic settings for 9 additional months (Fig. 3). No patients were allowed to have their PNS systems reactivated before completing this 3-month follow-up visit. However, patients were allowed to continue their baseline medication regimens throughout the study.

Surgical Procedure

Patients were taken to the operating room and positioned appropriately on the operating table for optimal access to the targeted nerve(s). Anesthesia of either the general or monitored anesthesia care (MAC) variety was induced. Electric clippers were used to shave the hair where appropriate, and the surgical site was prepared with isopropyl alcohol and chlorhexidine and covered with sterile drapes. Weight-based intravenous antibiotics, usually cefazolin, were administered prior to incision. For planning and measurement purposes, the electrode array was placed on the skin, with the distal electrode overlying the target nerve area. The first incision and needle entry point/pathway were planned using palpation and fluoroscopy. The skin and deeper tissues were anesthetized using local anesthetics at the initial introducer path. The first incision was made with a scalpel, and a 13-gauge introducer needle was passed through the incision and advanced in the fascial plane to the targeted nerve(s) area under image guidance, using small amounts of local anesthetic. One or a pair of 4-contact electrode arrays with tines or 8-contact electrode arrays without tines were inserted through the

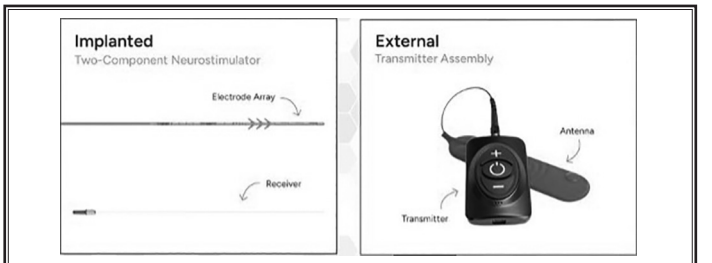

Fig. 2. *Freedom PNS System.*

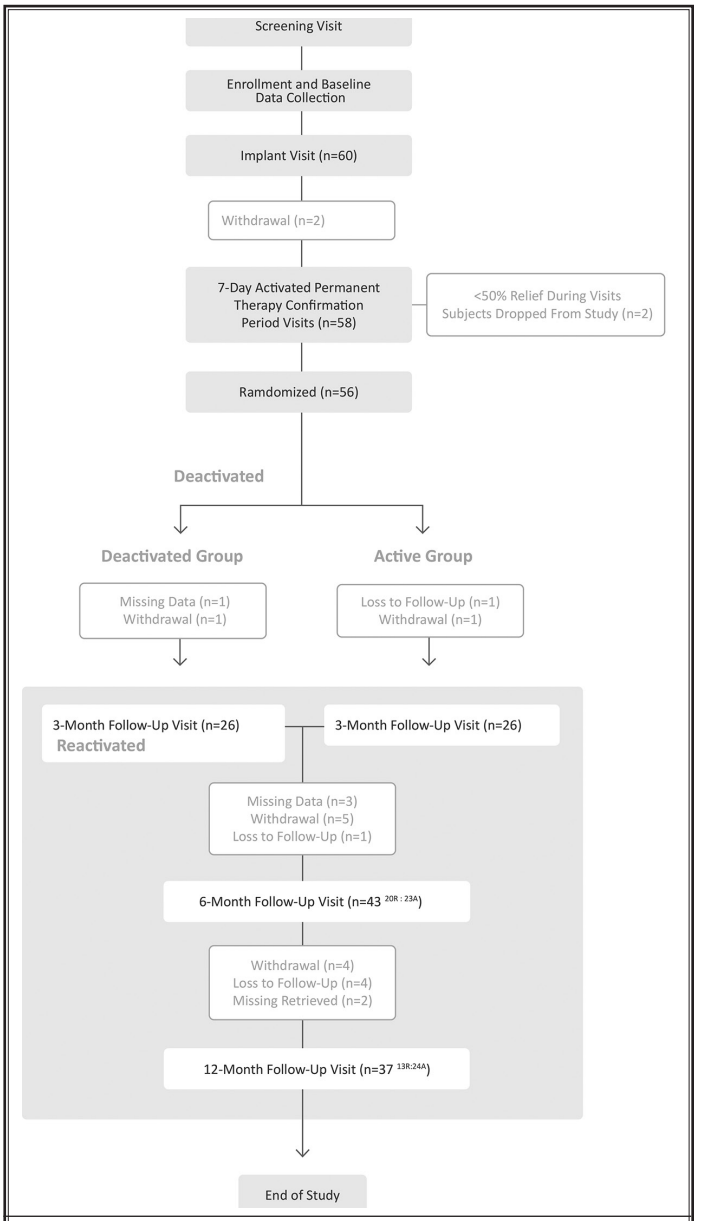

Fig. 3. *Flow chart and samples with attrition (CONSORT).*

cannula(s) and advanced to the targeted nerve(s) (Figs. 1 and 4).

A receiver pocket was created with the use of blunt dissection through a second distinct incision. The steering stylet was removed from the previously implanted electrode array, to which a separate receiver was then connected to the electrode array. After this connection, the electrode array and receiver were tunneled to the receiver pocket. Two nonabsorbable sutures were utilized to coil the receiver permanently. The end of the receiver coil was tucked underneath the rest of the coil to avoid protruding edges. Using a nonabsorbable suture, the receiver coil was sutured to the fascia in at least 2 locations, ensuring that the coil was flat in the pocket. The receiver pocket was closed with deep and superficial absorbable sutures.

Stimulation Parameters

At the time of implantation, patients were programmed with supra- and/or sub-paresthesia threshold stimulation pulse rates and variable intensity currents (mA).

After each patient received the implantation, the external transmitter antenna was worn over the receiver area. A wearable was utilized for that purpose. Patients were instructed to use stimulation for at least 8 hours daily during the initial 7-day therapy assessment period. Responders to stimulation during that first 7-day assessment period followed their randomization assignment to one of 2 arms: active or deactivated. Patients randomized to the active arm pursued stimulation with therapeutic settings for the remainder of the study (12 months). In contrast, the deactivated-arm patients had their systems deactivated for 3 months, after which they were allowed to resume active therapy with therapeutic settings for an additional 9 months.

Table 3. *Patient samples per site.*

Study Sites	Implanted Patients per Site
Site 1	6
Site 2	7
Site 3	7
Site 4	7
Site 5	9
Site 6	11
Site 7	13

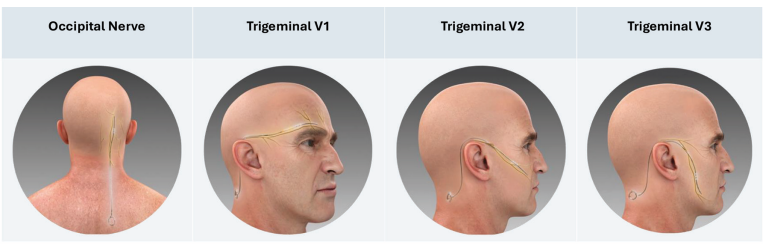

Fig. 4. *The figures provide examples of the 2-component neurostimulator (electrode array and separate receiver) implantation for the occipital nerve and trigeminal nerve branches.*

Data Collection and Analysis

Data were secured on case report forms and questionnaire instruments at the baseline and throughout the study. Data integrity was regulated via monitoring by an independent clinical research organization.

The statistical plan and associated analysis methods in this report were designed according to FDA requirements and submitted as part of a request for an IDE.

Three analysis samples were used in the study: the intent-to-treat (ITT), the modified ITT (mITT), and the secondary endpoint mITT. The ITT sample included all randomized patients (n = 60). The mITT sample included those in the ITT population who were followed up at 3 months after receiving permanent implants and whose primary endpoints were collected. Information on those patients was eventually used for the primary analysis (n = 52). Those patients who completed the 7-day assessment period successfully (at least a 50% pain reduction) and had reached the secondary endpoint in question at the 3-, 6- and 12-month follow-up times were the mITT sample for that endpoint. The sample size varied by endpoints at different follow-up terms.

The percentage of patients who experienced at least 50% pain reduction from the baseline 3 months after the first 7-day assessment period represented the primary effectiveness endpoint and was assessed for each treatment group. The success rate in the active group was compared to that in the deactivated group using Fisher's exact test of proportions at $\alpha = 0.05$.

The primary safety endpoint was evaluated 3 months after the initial 7-day assessment period. That endpoint consisted of an estimated objective percentage of patients who experienced at least one device-related (DR) or procedural-related (PR) serious adverse event (SAE),

described by the FDA as any undesirable experience associated with a patient's use of a medical product with an outcome of death, hospitalization, disability or permanent damage, congenital anomaly or birth defect, a threat to the patient's life, or required intervention to prevent permanent impairment or damage (20). Since both groups received permanent implants, the endpoint was computed in the combined treatment groups. The DR/PR-SAEs rate was evaluated by calculating the upper one-sided 95% confidence bound.

To establish sufficient statistical power for the primary effectiveness endpoint, the sample size was calculated to be 25 patients per treatment group. This sample size was estimated to provide at least 80% power in comparing the active arm to the deactivated arm at $\alpha = 0.05$, with at least 60% of the patients in the active arm reporting treatment success (at least 50% pain relief) and no more than 25% of the patients in the deactivated arm reporting the same. In the total study, to demonstrate with 95% confidence that the SAE rate was no higher than 5%, the total sample size required for the safety hypothesis was 60 patients. Therefore, 30 patients per treatment group became the sample size, and 60 became the total study size.

Six secondary endpoints with hypothesis tests were included; the observational endpoints did not include hypothesis testing. Each secondary hypothesis test included a 2-sided t-test of the inequality between active CFPNS treatment and deactivated treatment.

The secondary endpoints listed below were evaluated at 3, 6, and 12 months after the initial 7-day therapy assessment visit. Two different methods were employed to control the study-wise type I error. First, within each endpoint, there were 3 tests at each follow-up time. To maintain the endpoint-related follow-up at $\alpha = 0.05$, the method of Bonferroni was used: Each test was considered significant at $\alpha = 0.05/3 = 0.0167$. Then, to maintain the study-wise error rate at $\alpha = 0.05$ across all the endpoints, the hypothesis tests for secondary endpoint #2 were conducted only if at least one test of endpoint #1 passed at $\alpha = 0.0167$; the hypothesis tests for #3 were conducted only if at least one test of #2 passed.

The secondary endpoints included changes in the following order:

- Test 1: The visual analog scale (VAS) measures the patient's pain: The patient places a mark on a 0-100 mm scale on which 0 correlates to no pain and 100 correlates to the worst pain possible. Patients reported that they were focused on their craniofacial pain when they completed the VAS.
- Test 2: Brief Pain Inventory Facial (BPIF): A reliable and validated multidimensional tool that comprises 18 questions measuring 3 domains of pain: 1) pain intensity (worst and average pain intensity), 2) interference with general activities of daily living (ADL), and 3) face-specific pain interference.
- Test 3: Patient Global Impression of Change (PGIC): Measures the patient's impression of change in their condition since admission to the study. The PGIC was recorded at each follow-up point.
- Test 4: Quality of Life: Physical Component Score (PCS): Measures the quality of the physical dimension of life with a short-form questionnaire (SF-36).
- Test 5: Quality of Life: Mental Component Score (MCS): Measures the quality of the mental dimension of life with the SF-36.
- Test 6: Pain Rating Index (MPQ-SF-2): This short-form McGill Pain Questionnaire (MPQ) is a briefer version of the original MPQ. This tool may be used for standard registration and evaluation of an individual patient's complaints of pain. Furthermore, the MPQ-SF-2 can also be used for outcomes and to control the effects of therapies and/or pain relief in individual patients.

Results

Sixty patients were randomized and implanted with the Freedom PNS System (Curonix LLC): 30 in the active group and 30 in the deactivated group after the initial 7-day assessment period. Fifty-eight patients completed the 7-day assessment period successfully. (Two patients withdrew consent without completing the first post-implantation visit). Fifty-six out of 60 respondents, or 93%, experienced $\geq$ 50% improvement in VAS scores. Of those patients, twenty-eight had been randomized into the active permanent PNS group, and another 28 had been randomized to the deactivated permanent PNS group. Fifty-two patients (26 active, 26 deactivated, one missing, 2 withdrawals, and one lost to follow-up) completed the primary 3-month endpoint. After the deactivated group was reactivated, 43 patients in total (3 missing, 5 withdrawals, one lost to follow-up) completed the 6-month secondary endpoint, and 37 ([2 missing patients at 6 months were retrieved]; 4 withdrawals, 4 lost to follow-up) completed the 12-month endpoint (Fig. 3).

Baseline demographics and characteristics were compared between the 2 randomized treatment arms (Table 4). No statistically significant differences were

observed between the groups' baseline demographic characteristics. The mean age was 50.9 ± 15.4 in the active arm and 50.5. ± 14.8 years in the deactivated arm (P = 0.93). The active arm had 19 women and 11 men, compared to 16 women and 14 men in the deactivated arm (P = 0.44). The patients' mean pain durations were 19.1 ± 20.3 (active) and 21.3 ± 22.0 (deactivated) months before entering the study (P = 0.69). Baseline VAS scores differed significantly between both arms, with mean VAS pain scores of 78.4. ± 14.8 (active) and 68.3 ± 14.5 (deactivated) (P = 0.01); thus, the analysis used the change from baseline to accommodate that difference.

Primary Effectiveness Endpoint

The primary effectiveness endpoint (i.e., the proportion of patients experiencing at least 50% overall relief on a VAS scale) was compared between the active and deactivated groups at the 3-month period. The responder rate was 11% in the deactivated arm and 69% in the active group (Fisher's exact test $P < 0.001$). The primary effectiveness endpoint passed the inequality test, demonstrating that the proportion of responders was significantly larger within the active arm than in the deactivated arm. The estimated difference in responder rates was 58%, signifying that 58% more patients in the active group experienced clinically important relief with stimulation as compared to patients in the deactivated group (Table 5).

Primary Safety Endpoint

At 3 months, the primary safety objective evaluated the SAE rate in the combined groups. Throughout the entire study, no SAEs were reported. The safety analysis thus shows that the rate of SAEs is no higher than 5% with 95% confidence (Table 6).

Secondary Endpoints

The secondary objectives for both groups were tested, given that the primary analysis passed the hypothesis test.

The active-arm patients experienced a mean VAS reduction of 62%; by comparison, the deactivated arm experienced a mean reduction of 8.5% ($P < 0.001$) 3 months after the initial 7-day assessment period. The differences between the treatment groups were no longer statistically significant at 6 and 12 months after the initial 7-day therapy assessment period due to the reactivation of the previously deactivated group (Fig. 5).

Similar results were noted for the BPIF, PGIC, PCS, MCS, and MPQ-SF-2. At 3 months after the initial 7-day

Table 4. *Demographic information (mean age, height, weight, gender) and baseline characteristics of patients (months since onset of pain, baseline VAS score).*

	Active			Deactivated			*P*
	n	Mean	SD	n	Mean	SD	
Age (yr)	30	50.9	15.4	30	50.5	14.8	0.9
Height (in)	27	70.5	20.8	26	68.4	5.8	0.6
Weight (lb)	28	188.9	40.8	27	185.7	50.0	0.8
Months since onset	29	19.1	20.3	30	21.3	22.0	0.7
Baseline VAS	30	78.4	14.8	30	68.3	14.5	0.01
Gender	30	1.6	0.5	30	1.5	0.5	0.4
Male	11	36.7%	48.2%	14	46.7%	49.9%	NA
Female	19	63.3%	48.2%	16	53.3%	49.9%	NA

Table 5. *Proportion of patients who experienced greater than 50% pain relief at 3 months and the hypothesis test results.*

Analysis	Treatment	Population	n	Proportion of Responders	Test	*P*-value
mITT*	Active	mITT*	26	0.7	Fisher's exact	< 0.001
	Deactivated		26	0.1		
ITT**	Active	ITT**	30	0.6	Fisher's exact	< 0.001
	Deactivated		30	0.1		

*mITT: modified Intent-To-Treat
**ITT: Intent-To-Treat

assessment period, all secondary endpoints evinced statistically significantly greater improvements for the active arm as compared to the deactivated arm (Table 7).

Despite the 3-month hiatus taken by the deactivated arm, when stimulation was resumed, those patients reported the same degree of improvement that they did during the initial 7-day assessment period after their initial permanent implant procedures.

Observational Safety Endpoint

The most common nonserious adverse event (n = 17) was pain at the implant site and along the track of the neurostimulator. This result is to be expected in patients with implants in the craniofacial region (Table 8). Adverse events were logically comparable in both groups, since all patients received the same permanent PNS implant procedure.

Summary and Perspective

The primary efficacy analysis in this study measured the responder rate at 3 months after the 7-day assessment period to HF-EMC–powered permanent PNS in the craniofacial region. Of those who responded during the initial 7-day assessment period (mITT population), 69% were in the active group, but only 11% were in the deactivated group. Among all randomized patients (the ITT population), 60% were responders in the active arm, confirming the efficacy of the treatment. When the treatment for the deactivated group was reactivated, the levels of their pain relief returned to ≥ 50% improvement, which was seen previously during the 7-day assessment period, and mirrored the active group, confirming the durability of the stimulation effect.

The safety analysis demonstrated that the rate of SAEs at 3 months was significantly lower than 30%. In fact, no SAEs occurred during the study. The upper one-sided 95% confidence bound at the rate of 0.0% was 4.9%. The most commonly observed AE was pain at the implant site, which was to be expected with craniofacial implants.

The secondary objectives proved that active permanent PNS was superior to non-stimulation up to 3 months after the 7-day assessment period, when the deactivated population was reactivated. The VAS pain scale analysis showed significantly less pain in the active group than in the deactivated group at the 3-month follow-up visit. However, once the deactivated group was reactivated, there were no differences in pain relief at 6 and 12 months compared to the active group. Additionally, significant differences were found with the BPIF (general and facial), PGIC, QoL PCS and MCS, and MPQ-SF-2 (McGill Pain Questionnaire) tests between the active and deactivated groups at 3 months. Those discrepancies became equivalent once the deactivated group was reactivated.

The prominence of the *P*-value in this study and its statistical significance are considered to overcome performance bias, due to lack of blinding.

Discussion

This study examined the safety and efficacy of an HF-EMC–powered permanent PNS system in treating refractory chronic neuropathic craniofacial pain. Due to the delicate nature of implanting a PNS device in the craniofacial region, consenting patients who fulfilled the study eligibility criteria were implanted permanently without going through a traditional temporary trial procedure, thus avoiding additional procedures. After an initial permanent PNS implantation and successful therapy assessment period of one week, pa-

Table 6. *Primary safety endpoint.*

Analysis	Population	n	Kaplan-Meier Estimated Proportions		Upper One-Sided 95% Confidence Bound	
			SAEs	AEs	SAEs	AEs
mITT	mITT	56	0.0	0.43	0.05	0.55
ITT	ITT	60	0.0	0.4	0.05	0.51

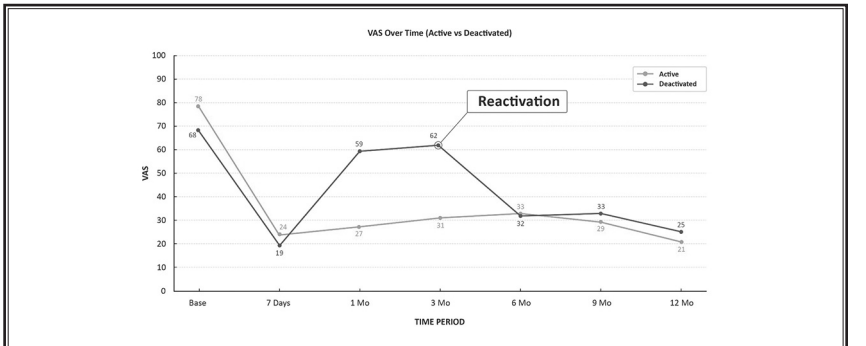

Fig. 5. *VAS reduction in the active vs. deactivated/reactivated arm.*

Table 7. *Changes in secondary endpoint scores for the mITT at 3, 6, and 12 months, with the results of their respective statistical analyses.*

	Time* (Mo)	Treatment	n	Mean Change from Baseline	Test	*P*-value*
VAS	3	Active	26	62%	t-test	< 0.001
		Deactivated	26	8.5%		
	6**	Active	23	61%	t-test	0.5
		Reactivated	20	53%		
	12**	Active	24	74%	t-test	0.3
		Reactivated	13	62%		
BPIF	3	Active	26	3.6	t-test	< 0.001
		Deactivated	26	0.1		
	6**	Active	22	3.5	t-test	0.2
		Reactivated	20	2.3		
	12**	Active	24	3.9	t-test	0.2
		Reactivated	13	2.8		
PGIC	3	Active	26	4.9	t-test	< 0.001
		Deactivated	26	1.7		
	6**	Active	23	5.4	t-test	0.5
		Reactivated	20	5		
	12**	Active	24	5.8	t-test	0.4
		Reactivated	13	5.3		
PCS	3	Active	26	-6.7	t-test	0.02
		Deactivated	26	-1.9		
	6**	Active	23	-7.3	t-test	0.9
		Reactivated	20	-7.0		
	12**	Active	24	-9.0	t-test	0.6
		Reactivated	13	-10.4		
MCS	3	Active	26	-6.1	t-test	0.01
		Deactivated	26	2		
	6**	Active	23	-6.7	t-test	0.27
		Reactivated	20	-2.7		
	12**	Active	24	-6.4	t-test	0.6
		Reactivated	13	-4.0		
MPQ-SF-2	3	Active	26	2.7	t-test	< 0.001
		Deactivated	26	-0.9		
	6**	Active	23	2.9	t-test	0.005
		Reactivated	20	1.1		
	12**	Active	24	2.7	t-test	0.04
		Reactivated	13	1.2		

* To account for multiple tests within an endpoint, *P*-values ≤ 0.0167 pass the hypothesis test and demonstrate statistical significance.
** The treatment for the deactivated group was reactivated after the 3-month visit.

tients were randomized to receive active stimulation (active group) or had the stimulation turned off for 3 months (deactivated group). Significant differences in primary and secondary outcome measures occurred between the active and deactivated groups during that 3-month period. The active group experienced much

Table 8. *Adverse events*.

	Active	Deactivated	All Patients (Active+Reactivated)	Resolved at 12 Months
Treatment-Related AE	≤ 3 Mo	≤ 3 Mo	>3 Mo	
Events	16	16	18	48/50 (96%)
Patients (n, %)	12, 40%	11, 37%	14, 23%	
Type of Adverse Event	≤ 3 Mo	≤ 3 Mo	>3 Mo	
Pain	5	6	6	(16/17)* 94%
Erosion	2	3	6	(11/11) 100%
Lead Migration **	2	1	4	(7/7) 100%
Device Failure	2	1	1	(4/4) 100%
Increased Stimulation	1	1	1	(3/3) 100%
Infection	2	1	0	(3/3) 100%
Other (Bruising (2), Itching (3))	2	3	0	(4/5)* 80%

*One event resolution unknown at 12 months.
**As verified by x-ray.

more significant pain relief than did the deactivated group, the patients in which had pain scores comparable to the baseline. The deactivated group regained pain relief with the reactivation of the stimulation at the end of the 3 months.

Comparison to Previous Studies

Previously published craniofacial stimulation studies have focused primarily on migraines and occipital neuralgias (17). Most of these studies have observed targeted neurostimulation of the occipital nerve rather than craniofacial nerves. Additionally, earlier studies utilized battery-based pulse generator systems that were most often implanted in the torso region distant from the targeted nerve rather than a receiver-based system implanted near the targeted nerve. Of those studies involving systems that stimulated craniofacial nerves, the most common targets were branches of the trigeminal nerve. Johnson and Burchiel reported on their experience with 10 patients with refractory neuropathic facial pain who received supraorbital and/or infraorbital neurostimulation (21). Among those 10 patients, the etiology was post-traumatic in 5, postherpetic in 4, and refractory V1 trigeminal neuralgia in one. CFPNS resulted in at least 50% pain relief in 70% of the patients, with decreased analgesic medication use and a high patient satisfaction rate. Mechanical complications related to lead connectors occurred in 30% of the patients, requiring surgical intervention. Stidd et al reported 2 cases of patients with trigeminal neuropathic pain (V1 and V2 branch target) and one case of postherpetic neuralgia (V1 branch target) who were treated with 2 percutaneous leads at the trigeminal nerves connected to a battery-based pulse generator system (22). Two patients with trigeminal neuropathic pain reported 100% pain relief with no complications, while the patient with postherpetic neuralgia experienced 60% pain relief and electrode migration that required revision. Weiner observed long-term efficacy in 12 patients with occipital neuralgia, reporting good to excellent response with pain control exceeding 50% and requiring little or no additional medication (23). Finally, Dunteman was able to conclude that peripheral nerve stimulation was successful in the treatment of 2 patients with postherpetic ophthalmic neuralgia (24).

The use of occipital nerve stimulation for treating refractory occipital neuralgia has been well studied. An extensive review by Sweet et al that included articles on the topic published between 1966 and 2023 recommended the use of occipital nerve stimulation for refractory cases (25).

Advantages of HF-EMC–Powered Permanent PNS

There are several advantages of an HF-EMC powered permanent PNS system. Although the physician's work is the same, one major advantage is the absence of the need to implant a battery-based pulse generator system in the trunk area (26,27). The utilization of a flexible receiver-based system is advantageous, since it allows physicians to adapt and conform the implant position to these challenging and unique craniofacial locations. This product design also reduces the risk associated with the placement of pulse generator devices

and the potential need for additional revision surgeries in this complex anatomical area (27,28). Additionally, the placement of an electrode array near highly mobile joints can increase the risks of migration, lead fracture, and the electrode array disconnecting from the pulse generator. The craniofacial region is highly mobile, specifically near the cervical occipital and temporomandibular joints innervated by the trigeminal nerve's mandibular branch (29). In a 2017 study by Weiner, another receiver-based PNS system placed directly adjacent to affected craniofacial nerve(s) proved to be a safe, reversible, and appropriate method of pain control for patients with craniofacial pain refractory to conventional medical managements (30). The efficacy and safety of this system, as reported in the CFPNS study, aligned with these earlier studies.

Limitations

One limitation in this study was the lack of a true placebo opportunity for this patient population (though the deactivated arm was designed to act as a control). Another was the absence of blinding, due to the use or no use of the external transmitter per design and the occasional utilization of supra-threshold stimulation (as well as sub-threshold stimulation). Finally, the COVID-19 pandemic had an impact on patient follow-up.

Conclusion

This RCT operated under an FDA IDE providing regulatory oversight. This landmark study confirmed that the HF-EMC powered permanent PNS system was a safe and efficacious modality for treating chronic craniofacial nerve pain. The results demonstrated significant pain reduction in implanted patients without reports of serious adverse events. This study provides Level I randomized control trial data, further contributing to the broad body of published long-term clinical evidence for the permanent Freedom PNS System.

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Supplemental material available at www.painphysicianjournal.com

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Appendix 1. *Inclusion and exclusion for the CFPNS study.*

Inclusion Criteria

A. Patient is ≥ 18 years of age at the time of informed consent;
B. Patient is diagnosed with craniofacial neuropathic pain with an average PRS (Pain Rating Scale) score > 5 (on a 0-10 scale), based on the baseline pain diary;
C. Patient's diagnosis of craniofacial neuropathic pain refractory to conventional medical management has been present for at least 12 months before enrollment;
D. Patient has been diagnosed with neuropathic pain in target areas by physical exam, which has detected the presence of hyperalgesia, allodynia, or partial sensory deficit;
E. Patient has failed to obtain pain relief from at least 2 different classes of medication;
F. Based on the medical opinion of the principal investigator, the patient had a stable pain medication regimen for 3 months before study entry;
G. Based on the medical opinion of the principal investigator, the patient had a stable tricyclic antidepressant regimen for 3 months before study entry;
H. Based on the medical opinion of the principal investigator, the patient has a stable opioid regime with a daily dose of < 30 mg of a morphine equivalent;
I. Based on the medical opinion of the principal investigator, there is no evidence of medication overuse, and the neuropathic pain is not attributed to a causative disorder;
J. Based on the medical opinion of the principal investigator, there is no evidence of anatomical abnormalities that could jeopardize the placement of the device or pose a hazard to the patient;
K. Based on the medical opinion of the principal investigator, the patient is willing and able to operate the Freedom® PNS System and has the ability to undergo study assessments and provide accurate responses;
L. Based on the medical opinion of the implanter, the patient is a good surgical candidate for the procedure;
M. Patient is willing to undergo surgical implant procedure, attend follow-up visits as scheduled, and comply with the study requirements;
N. Female patients of childbearing potential are not pregnant and agree not to become pregnant during the course of the study;
O. Patient is deemed to be neuropsychologically appropriate for implantation therapies based on an assessment by a clinical psychologist, using face-to-face encounters and psychological testing measures;
P. Patient has provided written informed consent using a form approved by the reviewing IRB.

Exclusion Criteria

A. Patient has undergone botulinum toxin (Botox) injections of the head and/or neck in the last 3 months;
B. Patient has had unresolved malignancies in the last 6 months;
C. Patient has a history of migraine, headaches of central origin, or trigeminal autonomic cephalalgias;
D. Patient has been diagnosed with acute shingles;
E. Patient has complete deafferentation of all branches of the trigeminal and/or occipital nerves;
F. Patient has been diagnosed with anesthesia dolorosa;
G. Patient has an active systemic infection, has multiple illnesses, or is immunocompromised;
H. Based on the medical opinion of the principal investigator, psychologist, and/or psychiatrist, the patient has other psychological conditions (e.g., psychosis, suicidal ideation, borderline personality disorder, somatization, narcissism), other health conditions (e.g., substance abuse, another chronic condition requiring the regular use of opioid medication), or other legal or medical concerns that would preclude his or her enrollment in the study or potentially confound the study results;
I. Patient is currently enrolled in or plans to enroll in a concurrent drug and/or device study while participating in this study;
J. Patient's bA1c levels are 7% or higher;
K. Patient has a known history of bleeding complications or coagulopathy issues;
L. Patient has a life expectancy of less than one year;
M. Patient has any active implanted device, whether turned off or on;
N. Patient has previous implanted stimulator experience for the treatment of craniofacial pain, including a failed trial or explanted device;
O. Patient has a condition requiring magnetic resonance imaging (MRI) evaluation or diathermy procedures;
P. Patient is currently involved in litigation regarding injury or is receiving worker's compensation benefits;
Q. Patient works regularly in environments with elevated levels of radiation or electromagnetic interference.