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Treatment of nonsurgical refractory back pain with high-frequency spinal cord stimulation at 10 kHz: 12-month results of a pragmatic, multicenter, randomized controlled trial

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OBJECTIVE Spinal cord stimulation (SCS) at 10 kHz (10-kHz SCS) is a safe and effective therapy for treatment of chronic low-back pain. However, it is unclear from existing evidence whether these findings can be generalized to patients with chronic back pain that is refractory to conventional medical management (CMM) and who have no history of spine surgery and are not acceptable candidates for spine surgery. The authors have termed this condition "nonsurgical refractory back pain" (NSRBP) and conducted a multicenter, randomized controlled trial to compare CMM with and without 10-kHz SCS in this population.

METHODS Patients with NSRBP, as defined above and with a spine surgeon consultation required for confirmation, were randomized 1:1 to patients undergoing CMM with and without 10-kHz SCS. CMM included nonsurgical treatment for back pain, according to physicians' best practices and clinical guidelines. Primary and secondary endpoints included the responder rate (≥ 50% pain relief), disability (Oswestry Disability Index [ODI]), global impression of change, quality of life (EQ-5D-5L), and change in daily opioid use and were analyzed 3 and 6 months after randomization. The protocol allowed for an optional crossover at 6 months for both arms, with observational follow-up over 12 months.

RESULTS In total, 159 patients were randomized; 76 received CMM, and 69 (83.1%) of the 83 patients who were assigned to the 10-kHz SCS group received a permanent implant. At the 3-month follow-up, 80.9% of patients who received stimulation and 1.3% of those who received CMM were found to be study responders (primary outcome, ≥ 50% pain relief; $p < 0.001$). There was also a significant difference between the treatment groups in all secondary outcomes at 6 months ($p < 0.001$). In the 10-kHz SCS arm, outcomes were sustained, including a mean 10-cm visual analog scale score of 2.1 ± 2.3 and 2.1 ± 2.2 and mean ODI score of 24.1 ± 16.1 and 24.0 ± 17.0 at 6 and 12 months, respectively ($p = 0.9$). In the CMM arm, 74.7% (56/75) of patients met the criteria for crossover and received an implant. The crossover

ABBREVIATIONS AE = adverse event; CLBP = chronic low-back pain; CMM = conventional medical management; EQ-5D-5L = EQ-5D 5-level; FBSS = failed back surgery syndrome; IPG = implantable pulse generator; ITT = intention to treat; MCID = minimal clinically important difference; NSRBP = nonsurgical refractory back pain; ODI = Oswestry Disability Index; PGIC = Patient-Reported Global Impression of Change; PP = per protocol; RCT = randomized controlled trial; SAE = serious AE; VAS = visual analog scale; 10-kHz SCS = spinal cord stimulation at 10 kHz.

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arm obtained a 78.2% responder rate 6 months postimplantation. Five serious adverse events occurred (procedure-related, of 125 total permanent implants), all of which resolved without sequelae.

CONCLUSIONS The study results, which included follow-up over 12 months, provide important insights into the durability of 10-kHz SCS therapy with respect to chronic refractory back pain, physical function, quality of life, and opioid use, informing the current clinical practice for pain management in patients with NSRBP.

Clinical trial registration no.: NCT03680846 (clinicaltrials.gov)

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KEYWORDS nonsurgical refractory back pain; pain management; spinal cord stimulation; low-back pain; high-frequency; 10-kHz SCS; lumbar

Chronic low-back pain (CLBP) is a common condition that affects an estimated 13.1% of the US population and is associated with higher levels of medical comorbidities, increased healthcare costs, and lost productivity.[1,2] According to current clinical guidelines, conventional medical management (CMM) for CLBP includes analgesic medications, physical therapy, nerve blocks, epidural steroid injections, radiofrequency ablation, and other therapies.[3–6] We use the terminology "nonsurgical refractory back pain" (NSRBP) to describe patients with chronic refractory back pain that does not respond to CMM and who have no history of spine surgery and are not acceptable candidates for surgery after evaluation by a spine surgeon. This term was first introduced in a publication by Patel el al.[7] There is an unmet need for safe and effective nonpharmacological therapy for NSRBP,[8] as currently there are few effective treatment options.[9]

Although evidence for the efficacy of spinal cord stimulation at 10 kHz (10-kHz SCS) in refractory CLBP is now substantial and of high quality, most patients included in these studies had a history of back surgery, and most were diagnosed with failed back surgery syndrome (FBSS).[10–13] "Failed back surgery syndrome" is an imprecise term generally understood to identify patients who have had back surgery at some point in the past and who have persistent back pain at the present time. While efforts to define more useful diagnosis-related identifiers are underway,[14] the FBSS term is used for consistency with referenced studies. A subanalysis of surgery-naive patients in the SENZA–randomized controlled trial (RCT) and SENZA-EU trials found efficacy results comparable with those of the full study cohort,[15] and a single-center, prospective, proof-of-concept study evaluating 10-kHz SCS treatment using a narrower definition of NSRBP showed profound and durable back and leg pain and functional capacity improvements (at the 3-year follow-up).[16,17]

Despite their supportive nature, these previous studies and analyses included only small numbers of patients with NSRBP, and additional high-quality clinical evidence is needed regarding both the efficacy and cost-effectiveness of treatment with 10-kHz SCS in these patients. The current multicenter RCT was designed to compare treatment via 10-kHz SCS and CMM with CMM alone.[7] The results of this study, including the primary and secondary endpoints and 12-month follow-up, are presented herein.

Methods

The design of this multicenter RCT has been described previously.[7] Patients for whom CMM had failed and had not undergone previous lumbar spine surgery were included after providing consent. Patients went on to randomization if they met all inclusion and exclusion criteria (Supplemental Table 1), with the main inclusion criteria being a diagnosis of chronic, axial, low-back pain with a neuropathic component and no previous spine surgery. In addition, each patient underwent a consultation with a spine surgeon, whereby they were deemed to be inappropriate candidates for spine surgery.

After meeting inclusion criteria, patients provided written informed consent for randomization and the potential for crossover. In the prespecified statistical plan, up to 216 patients were allowed to be randomized 1:1 to receive either CMM alone or 10-kHz SCS in addition to CMM. The randomization used permuted block sizes at each clinical site to help maintain balance in allocation. Randomization assignments were computer generated with a code provided by an independent statistician and allocated via the electronic data capture system.

The trial protocol[7] and reporting followed CONSORT guidelines[18] and included outcomes were concordant with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines.[19] The trial was registered at ClinicalTrials.gov (registration no. NCT03680846) prior to patient enrollment. The protocol and informed consent were approved by the Western Institutional Review Board and local site IRBs, as required. Collection of patient-reported outcomes and other data in both study arms were performed by clinic-employed personnel. Sponsor involvement of patient management was limited to technical recommendations and programming, as supervised by the investigator.

Treatment Groups

Patients randomized to 10-kHz SCS received a trial stimulation lasting up to 14 days, using 2 percutaneous leads with 8 contacts each, placed in the epidural space with final position spanning T8–11 fluoroscopic vertebral height. Paresthesia-independent stimulation was delivered at 10 kHz with a pulse width of 30 μsec, and the current amplitude was adjusted to maximize pain relief. While low-frequency SCS is thought to achieve pain relief by requiring activation of Aβ fibers in the dorsal column, generating paresthesia and indirectly affecting pain signaling, recent research has suggested that paresthesia-free pain relief obtained with 10-kHz SCS is achieved by inhibiting pain processing more directly in the spinal dorsal horn.[20] A successful SCS trial, which was defined as ≥ 50% pain

relief, was required for patients to be eligible for permanent implantation of the 10-kHz SCS device (Senza, Nevro Corp.).

Patients randomized to the CMM treatment group continued to receive the best standard of care as determined for each individual patient by the study investigator. Although not strictly prescribed, CMM was required to be generally consistent with clinical guidelines developed by the American College of Physicians and the American Pain Society, as well as the interventional pain management guidelines developed by the American Society of Interventional Pain Physicians.[6,21]

Follow-up visits with assessments were completed at 1, 3, 6, 9, and 12 months after randomization, with optional crossover available to patients in both arms after completing 6 months in the study.[7] Those patients opting to crossover at 6 months were required to meet the following criteria: < 50% pain relief from baseline, dissatisfaction with treatment, and investigator approval of medical appropriateness. The flow of patients through the study from baseline assessment through 24 months of follow-up is shown in Supplemental Fig. 1.

Study Flow

Pain intensity and pain relief were measured using a 10-cm visual analog scale (VAS). Pain responders were defined as those patients who reported pain relief ≥ 50%. This threshold has been used as the efficacy standard in most previous studies of SCS, including SENZA-RCT, SENZA-EU, and the pilot study conducted in patients with NSRBP.[10,11,17] Disability was assessed with the Oswestry Disability Index (ODI),[22,23] and we defined ODI responders as patients who had an improvement in ODI scores of ≥ 10 points, the minimal clinically important difference (MCID) for this validated measure.[24,25] The 7-point Patient-Reported Global Impression of Change (PGIC) was used to quantify the perception of functional change in response to study treatment.[26] Patient quality of life was evaluated using the EQ-5D 5-level (EQ-5D-5L) instrument score, which assesses changes in health-related quality of life along 5 dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[27] The MCID for the EQ-5D-5L varies depending on the patient population and disease state and is estimated to range from 0.037 to 0.069.[28] We used the upper end of this range, 0.069, as the MCID when analyzing the results of this study. Finally, daily opioid use was recorded in patient diaries by the subset of patients who entered the study on a regimen of prescribed opioids. These data were converted to the total daily milligram morphine equivalent to determine if opioid analgesic dosages changed in response to the study treatment.

The primary endpoint of this study was the responder rate (≥ 50% pain relief) at 3 months. There were 5 prespecified secondary endpoints that were tested hierarchically and that compared the following between the treatment and control groups at 6 months: 1) proportion of patients with a ≥ 10-point decrease in ODI score from baseline, 2) percentage change from baseline in back pain intensity (as assessed by the VAS-back), 3) proportion of patients reporting "better" or "a great deal better" on the PGIC, 4) mean change from baseline in the EQ-5D-5L, and 5) mean change in opioid medication usage.

Adverse events (AEs) were assessed at all visits, including follow-up visits and unscheduled visits, and any serious or treatment-related AEs observed by investigators or reported by patients were recorded. All serious AEs (SAEs) were reviewed by the principal investigator of the site in accordance with medical device reporting requirements.

As an additional safety outcome, a neurological assessment was performed at baseline and at 3-, 6-, and 12-month follow-ups, following the standard-of-care procedure at each investigator's practice. Neurological status included motor, sensory, and reflex functions, which were characterized as improved, maintained, or a deficit as compared with the baseline status.

Analysis

The assumptions resulting in an estimated sample size of 216 randomized patients were presented previously.[7] A single prespecified interim analysis was triggered when 40% of the planned study population reached the 3-month primary endpoint. The objective of the interim analysis was to assess the prespecified statistical assumptions of the sample size and determine if it was necessary to increase the sample size, stop the study for futility, or discontinue enrollment for already sufficient power.

The prespecified interim analysis indicated that the sample size was sufficient to show superiority of treatment for the primary endpoint; therefore, enrollment was stopped at 211 patients.

The intention-to-treat (ITT) population was defined as all randomized patients, and the per protocol (PP) population was defined as including only those patients (n = 68) who completed the last visit used in the analysis. For the primary endpoint analysis, Fisher's exact test was used to compare responder rates between the two treatment groups in the ITT population. Secondary endpoints were hierarchically tested in the PP population at the 6-month time point, with each endpoint tested in succession in the order listed above until statistical significance was not observed. Significance for difference between treatment arms in proportions of ODI responders and PGIC reporting was tested using Fisher's exact test. Changes in the mean VAS-back and EQ-5D-5L scores and daily opioid intake were analyzed using a 2-group, 2-sided, Student t-test. Levene's test for equality of variances was used and, when appropriate, equal variances was not assumed; p values of ≤ 0.05 were considered statistically significant. Independent biostatisticians performed all analyses, which were consistent with the prespecified statistical analysis plan.

Results

Patient Disposition

Study enrollment started on September 5, 2018, and ended on January 27, 2020, with 211 patients. Fifty-two patients did not meet inclusion criteria; thus, 159 patients were randomized 1:1 to either the CMM (n = 76) or 10-kHz SCS (n = 83) treatment arms. Of 83 patients randomized to the SCS arm, 80 underwent trial stimulations, 74

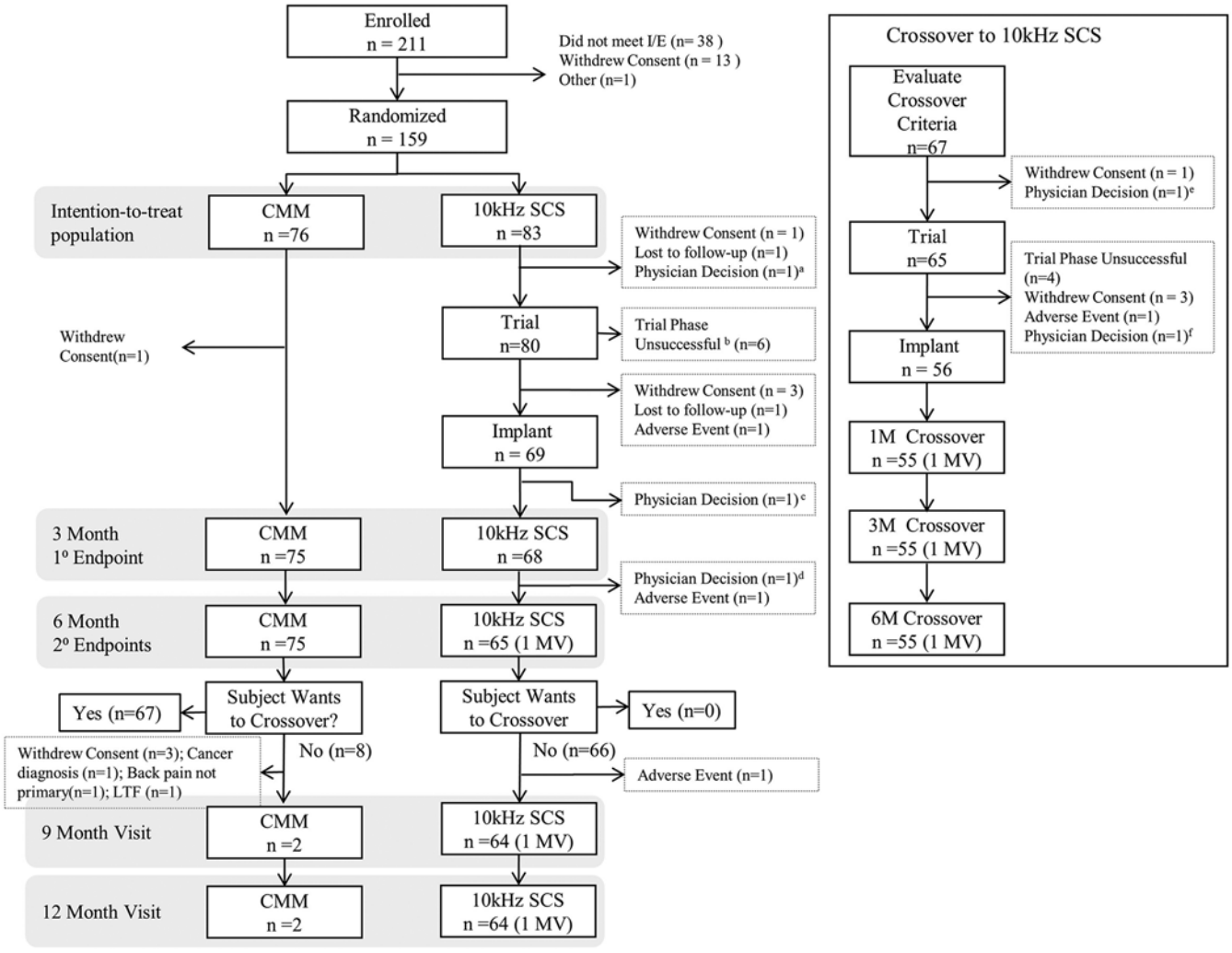

FIG. 1. Disposition of all enrolled patients in the study. [a] Concern about COVID-19 risk due to older age and multiple comorbidities. [b] Defined as < 50% pain relief. [c] Diagnosis of ruptured discs; study exit to seek surgical interventions. [d] Diagnosis of cervical myelopathy and subsequent cervical spine surgery. [e] Patient required hip surgery. [f] Perceived risk due to comorbidity. I/E = inclusion/exclusion criteria; LTF = lost to follow-up; MV = missed visit; 1M = 1 month; 3M = 3 month; 6M = 6 month; 1° = primary; 2° = secondary.

(92.5%) of whom had successful trials, and 69 patients ultimately received permanent implants (Fig. 1). No patients in the 10-kHz SCS arm crossed over, while 86.6% (65/75) elected to cross from CMM to 10-kHz SCS and proceeded with the trial stimulation. The trial success rate was 93.8% (61/65); there were 5 posttrial withdrawals, resulting in 74.7% (56/75) of the CMM arm receiving a permanent implant. The final patient completed the 12-month visit (or 6-month postcrossover visit) on June 9, 2021. A total of 125 (86.2%) of the 145 patients who proceeded to trial stimulation (the original 10-kHz SCS arm plus patients who crossed over) received a permanent implant. Study retention was high, with 121 of 125 patients (96.8%) remaining in the study through the 12-month follow-up.

Patient baseline demographics and clinical characteristics are shown in Table 1. The 2 treatment groups were similar in terms of age, sex, and race, and the mean pain scores and time since diagnosis were, likewise, comparable in both study arms. At baseline, all patients had CLBP and a median time since diagnosis of more than 8 years, and 97 patients (61%) had leg pain as well. A list of pain etiologies is shown, and the breakdown of etiologies in each treatment group is similar, with degenerative disc disease and spondylosis affecting a majority in each group. The groups were also similar in terms of the reasons that patients were not surgical candidates, as judged by spine surgeon evaluation prior to randomization. In both groups, approximately 80% of patients were not acceptable surgical candidates based on presentation and underlying pathology, and 20% of patients were nonsurgical because they declined surgery or were at moderate to high surgical risk due to comorbidities or other clinical conditions. It is important to note that inclusion criteria required that every patient be evaluated by a spine surgeon for surgical candidacy prior to randomization.

TABLE 1. Patient demographics and baseline clinical characteristics

	CMM (n = 76)	10-kHz SCS (n = 83)
Median age, yrs (range)	58.50 (26.0–77.0)	53 (29.0–87.0)
Sex F/M, n	40/36	50/33
Race, n (%)*		
White	73 (96.1)	75 (90.4)
Black or African American	2 (2.6)	4 (4.8)
American Indian or Alaska Native	1 (1.3)	2 (2.4)
Asian	0	2 (2.4)
Native Hawaiian or other Pacific Islander	0	1 (1.2)
Other	0	1 (1.2)
Median time since diagnosis of CLBP, yrs (range)	8.00 (1.0–59.0)	8.50 (0.5–52.0)
VAS pain score-back		
Mean (SD)	7.2 (1.0)	7.4 (1.2)
Median (range)	7.2 (4.5–9.9)	7.6 (4.0–10.0)
Baseline leg pain present†	45 (59.2)	52 (62.7)
Pain etiology, n (%)*		
Degenerative disc disease	52 (68.4)	60 (72.3)
Internal disc disruption/annular tear	6 (7.9)	8 (9.6)
Spondylosis	49 (64.5)	55 (66.3)
Lumbar facet-mediated pain	25 (32.9)	24 (28.9)
Radiculopathy	35 (46.1)	34 (41.0)
Mild/moderate spinal stenosis	24 (31.6)	23 (27.7)
Spondylolisthesis	9 (11.8)	7 (8.4)
Sacroiliac dysfunction	5 (6.6)	3 (3.6)
Total painDETECT scores‡		
Mean (SD)	17.2 (7.4)	17.8 (6.9)
Median (range)	17.5 (0.0–37.0)	18.0 (1.0–33.0)
Nonsurgical candidate reason, n (%)		
Not a good surgical candidate based on presentation & underlying pathology	61 (80.3)	65 (78.3)
Candidate for surgery but declined	10 (13.2)	11 (13.3)
Not recommended due to moderate to high surgical risk related to comorbidities or other clinical conditions (e.g., smoking, obesity, or chronic heart failure)	5 (6.6)	6 (7.2)

* Patients may have > 1 race or pain etiology reported.
† Only patients with a left or right lower-limb baseline pain score ≥ 5.
‡ painDETECT is a patient-reported assessment of neuropathic pain. Scores range from −1 to 38, with scores ≥ 19 indicating the likelihood (> 90% probability) that the patient has neuropathic pain.

Primary Endpoint

The results of the primary endpoint analysis are shown in Fig. 2A. Results in the PP population showed that 55 patients (80.9%) treated with 10-kHz SCS were responders, significantly more than the single responder (1.3%) in the CMM group ($p < 0.001$). The results obtained using the ITT analysis were similar in the CMM arm (1.3%) while 74.3% of patients in the 10-kHz SCS arm were responders ($p < 0.001$).

Secondary Endpoints

Outcomes of the secondary endpoints analyzed at 6 months are summarized in Table 2, including the crossover group at 3 and 6 months postimplantation. Disability was assessed by ODI scores, and the mean ODI score for patients in the 10-kHz SCS treatment group decreased 24.2 points at the 3-month follow-up, in the range of moderate disability levels, and the mean 6-month score was 22.7 points lower than baseline. ODI scores in the control group, in contrast, did not significantly change from baseline through 6 months. The MCID for ODI scores used in this study is 10 points,[24,25,29] and patients who had ODI score decreases of ≥ 10 points were defined as ODI responders. Approximately two-thirds of patients in the treatment arm were ODI responders after 1 month of stimulation, and 78.5% were responders at 6 months (Fig. 2B). In comparison, 4% of patients in the CMM arm were ODI responders after 6 months.

The next secondary outcome to be tested, the mean pain score, declined by 72% in patients who received 10-kHz SCS after 6 months of treatment, yet rose 6% in those who received CMM alone ($p < 0.001$). These pain relief results were supported by other secondary outcomes, in-

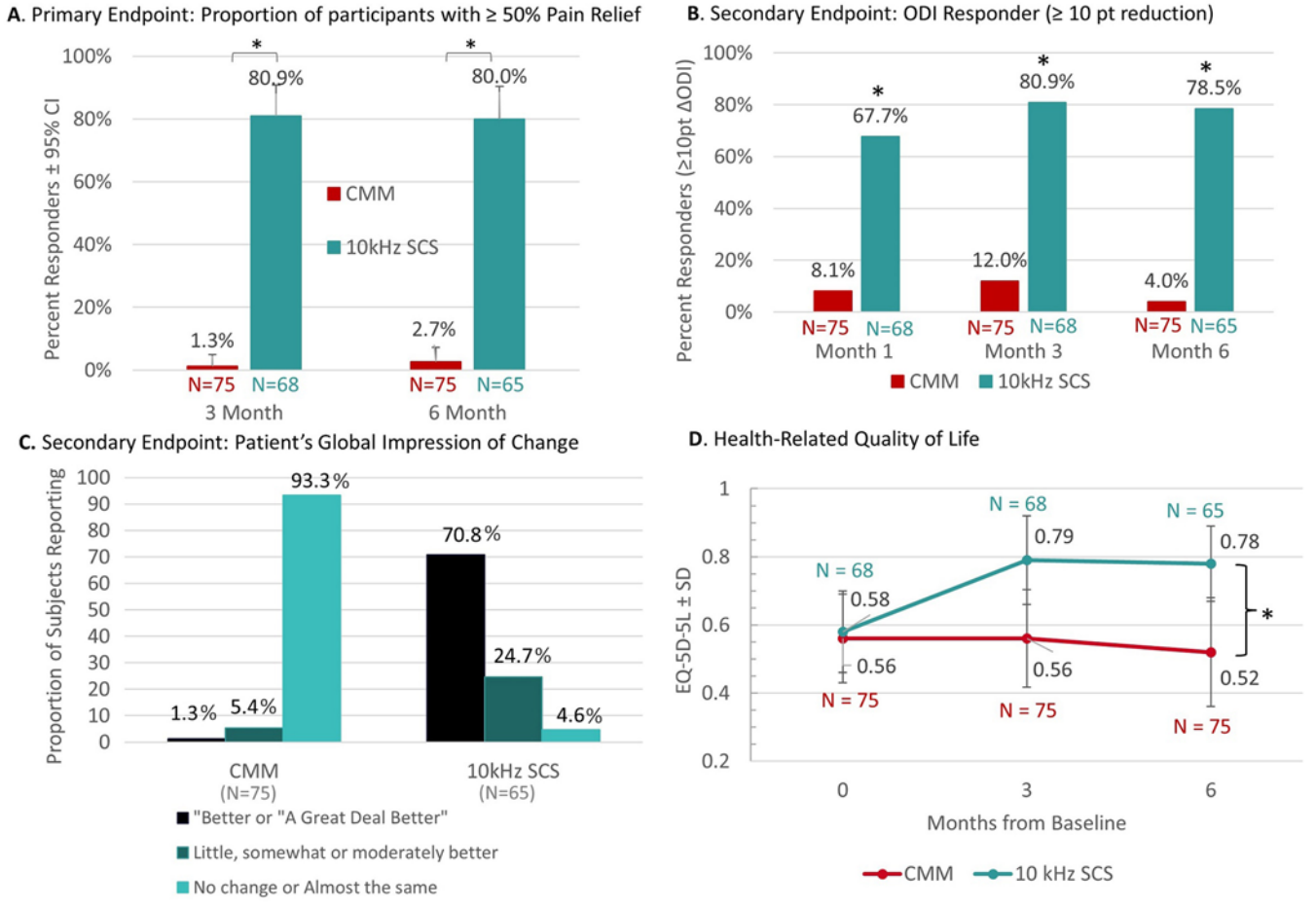

FIG. 2. Bar graphs showing a comparison between groups for the primary and secondary outcomes. **A:** The responder rates for pain relief (≥ 50% reduction in the VAS score) at 3 and 6 months. **B:** ODI responder rates (percentage of patients with a ≥ 10-point decrease) at 3 and 6 months. **C:** Distribution of patient responses on the PGIC. **D:** Change between baseline and 6 months in reported quality of life as measured by the EQ-5D-5L. *p < 0.001 for between-group comparison with the Fisher's exact test. Figure is available in color online only.

cluding reported PGIC scores, which revealed that 1.3% of patients who received CMM perceived that their condition was "better" or "a great deal better" after 6 months of treatment (Fig. 2C); 70.8% of patients who received 10-kHz SCS reported the same. Changes in patient quality of life, as assessed by the EQ-5D-5L index score, are shown in Fig. 2D. Mean EQ-5D-5L scores were similar at baseline but rose 0.20 points after 3 months of treatment in patients who received 10-kHz stimulation, and this increase was maintained through 6 months. This change was nearly 3 times the MCID for the index score and was significantly higher than the mean score for control patients at 6 months.

Finally, in patients receiving opioids (52.1% of the PP population), the mean daily intake in the 10-kHz SCS treatment group decreased on average by 45.8% at the 6-month follow-up compared with baseline usage, while the mean opioid intake of the control patients increased on average by 12.1% over the same period (Fig. 3A). After 6 months of treatment, 21.9% (7/32) of patients who received 10-kHz stimulation had stopped taking opioid analgesics altogether and a further 44% (14/32) of patients experienced a decrease in their daily dose, while 17.1% (7/41) of control patients experienced a decrease in their analgesic intake and none had stopped taking opioids completely (Fig. 3B).

Individual pain relief is shown in Fig. 4. A total of 52 patients in the treatment group (80.0%) were pain responders (≥ 50% pain relief) at the 6-month follow-up, significantly more than the 2 responders in the CMM group (2.7%). The proportion of patients who reported profound pain relief, defined as ≥ 80% reduction in pain, was 58.5% among patients who received SCS and 0% in the control group. This responder rate was stable over the 12 months of follow-up in the treatment group, with 78.2% of patients (50/64) as responders. The responder rate at 6 months in the crossover group was equivalent to the original treatment group at 78.2% (43/55).

The primary and secondary reported outcomes all showed durability to the 12-month follow-up in the 10-kHz SCS group (Fig. 5). The mean reported back and leg pain scores over the 12 months of follow-up are shown in Fig. 5A, with both sustaining a mean VAS score < 2.5 cm.

TABLE 2. Secondary endpoints evaluated 3 and 6 months postbaseline for both randomized arms and crossovers

Outcome	CMM		10-kHz SCS			Crossovers to 10-kHz SCS†		
	Value	Total No. of Pts	Value	Total No. of Pts	p Value*	Value	Total No. of Pts	p Value‡
ODI responder, n (%)§								
3 mos	9 (12)	75	55 (80.9)	68	<0.001	42 (76.4)	55	0.0976
6 mos	3 (4)	75	51 (78.5)	65	<0.001	43 (78.2)	55	0.5242
Mean % change in VAS pain score-back (SD)								
3 mos	0.41 (20.8)	75	–74.1 (25.9)	68	<0.001	–64 (33.3)	55	0.6578
6 mos	6.2 (21.7)	75	–72 (32)	65	<0.001	–70.4 (29.2)	55	0.8252
PGIC improvement (better or a great deal better), n (%)								
3 mos	1 (1.3)	75	47 (69.1)	68	<0.001	NC		0.4469
6 mos	1 (1.3)	75	46 (70.8)	65	<0.001	36 (65.5)	55	0.5599
Mean change in EQ-5D-5L score (SD)								
3 mos	0.004 (0.150)	75	0.207 (0.136)	68	<0.001	0.179 (0.131)	55	0.3376
6 mos	–0.042 (0.144)	75	0.201 (0.126)	65	<0.001	0.182 (0.135)	55	0.5391
Mean change in daily opioid dose, MME (SD)								
3 mos	4.9 (12.9)	41	–13.5 (30)	33	<0.001	–2.9 (39.5)	29	0.2448
6 mos	1.0 (10.8)	42	–17.7 (27.0)	32	<0.001	–5.7 (44.1)	28	0.2148

MME = milligram morphine equivalent; NC = not collected.
* Comparison between randomized groups.
† Time interval represents months postimplant for crossover group.
‡ Comparison between 10-kHz SCS arm and crossovers.
§ ODI responder is defined as those patients with ≥ 10-point reduction in ODI score compared with their baseline score.

The ODI total score remained at a 22.5 (SD 16.4) point reduction from baseline to 12 months (Fig. 5B), and the EQ-5D-5L index score remained 0.20 (SD 0.15) points above baseline (Fig. 5C), both mirroring the pain outcome. The average percent change in opioid daily dose from baseline is shown in Fig. 5D, which was a statistically significant reduction at all time points ($p < 0.05$), with the reduction remaining at an average 49.6% at 12 months.

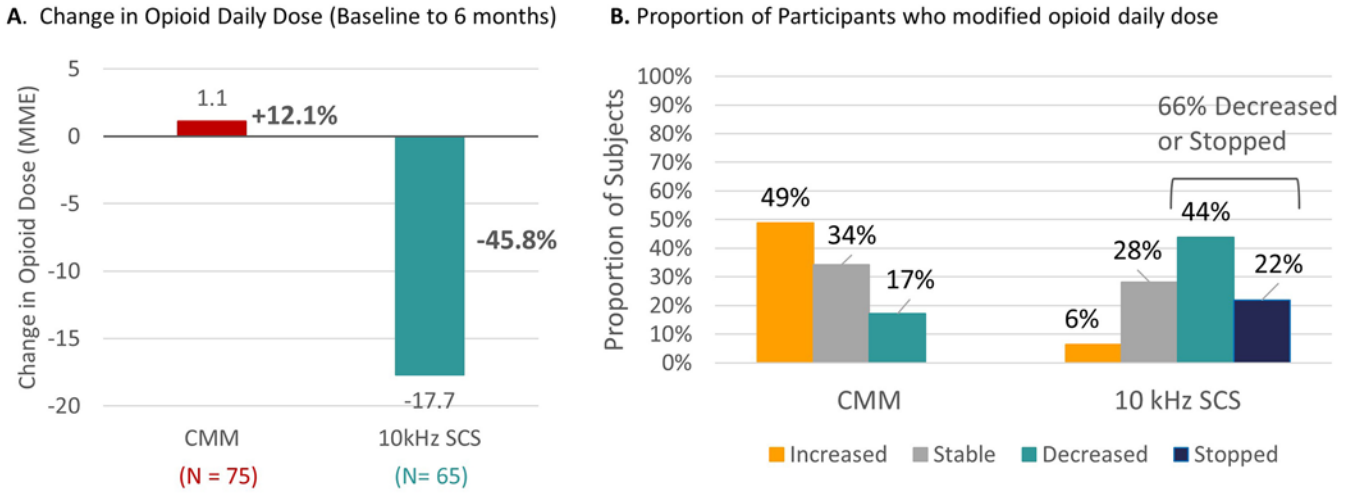

FIG. 3. A: Bar graph showing the change in daily opioid dosage (milligram morphine equivalent [MME]) for both treatment groups from baseline to 6 months of treatment. **B:** Bar graph showing the treatment groups broken down by the proportion of patients increasing, decreasing, stopping, or maintaining their daily opioid dose from baseline to the 6-month follow-up; 66% of patients in the 10-kHz SCS group had a decreased dose or stopped receiving opioids between baseline and 6 months. Figure is available in color online only.

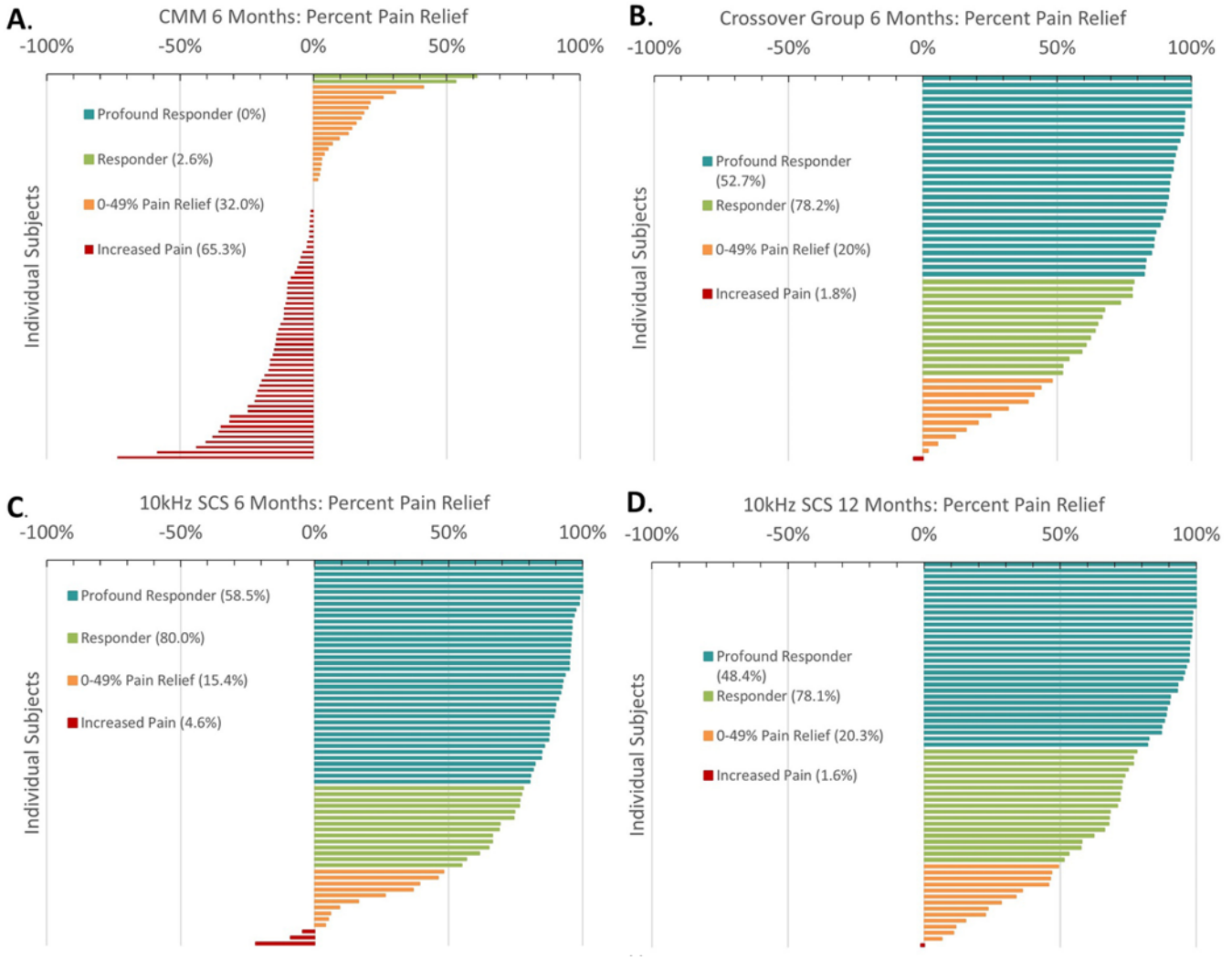

FIG. 4. Individual pain relief, as measured by VAS scores, is shown with the patients having the most pain relief at the top of the tornado plots and the patients reporting the least pain relief at the bottom. The color coding indicates the level of pain relief, with the legend including the percentage of patients at that level of pain relief. Responder indicates ≥ 50% pain relief, and profound responder indicates ≥ 80% pain relief. **A:** CMM-alone arm at 6 months. **B:** 10-kHz SCS treatment arm at 6 months. **C:** Crossover to 10-kHz SCS cohort at 6 months postimplantation. **D:** Randomized 10-kHz SCS arm at 12 months. Figure is available in color online only.

Safety Outcomes

The study-related AE occurrence in the 145 patients who underwent trial stimulation (both the original 10-kHz SCS arm and the crossover group) was 41 AEs, which occurred in 35 patients (24.1%), including 36 (87.8%) of 41 AEs that were either mild or moderate in severity. The most common AE was implant site pain, reported by 7 patients (4.8%), of whom 3 (2.0%) required implantable pulse generator (IPG) repositioning. Implant site infection was reported by 5 patients (3.4%), and 3 patients (2.0%) had transient CSF leakage. Five patients (3.4%) underwent lead revisions, 3 due to lead dislodgment and 2 due to lack of therapeutic effect.

A total of 5 study-related SAEs was reported in the combined cohort (all patients who received an implant) and all were procedure related (Table 3). There were 2 patients (1.4%) with infections resulting in explantation, both of whom underwent reimplantation after the infection resolved. All SAEs resolved without sequelae. Notably, there were no explantations due to lack of therapeutic effect. The majority of patients in both groups maintained their neurological status on motor, sensor, and reflex assessments. There were 3 cases of a deficit in the CMM group, motor (n = 1) and sensory (n = 2), at 3 months, with 1 sensory deficit remaining at 6 months. One sensory deficit was reported in the 10-kHz SCS group at 3 months, which was attributed to stimulation. The stimulation was adjusted and the sensory deficit resolved. No deficits were reported in the 10-kHz SCS arm at 6 or 12 months. Improved performance on standard neurological assessments was observed in 16.9% of patients (n = 11) who received 10-kHz SCS and for a single patient in the CMM arm. Improvement was statistically significant (p = 0.001, 2-sided Mann-Whitney U-test), and most were

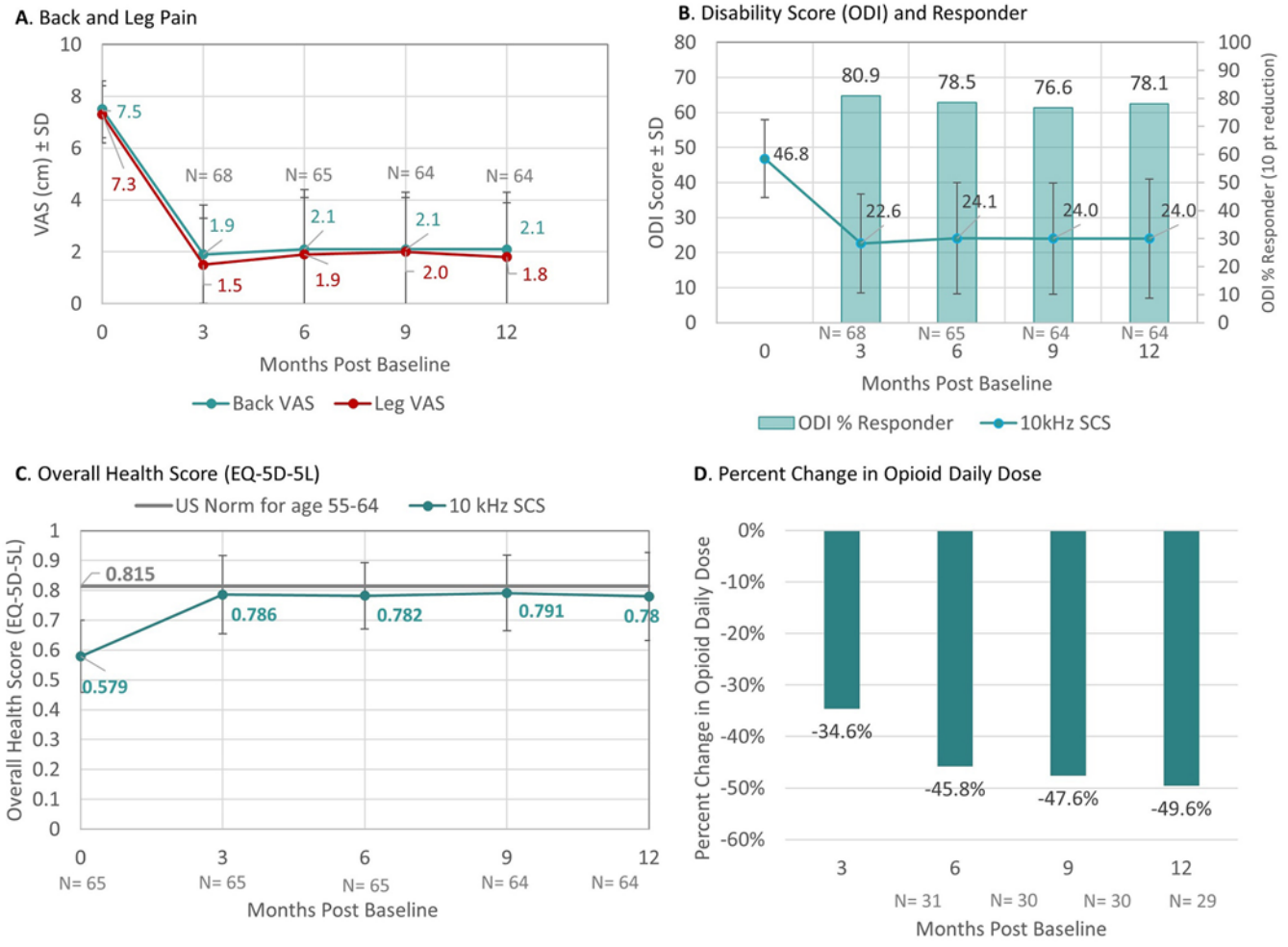

FIG. 5. Secondary outcome trends to 12 months in the 10-kHz SCS arm, including back and leg pain (VAS) (**A**), disability score (ODI) (**B**), overall health score (EQ-5D-5L) (**C**), and percentage change in opioid daily dose (**D**). At the 12-month follow-up, the mean reported VAS-back score was 2.1 ± 2.2 cm, corresponding to reduction of 72% from baseline. Figure is available in color online only.

observed in the motor assessment portion of the neurological examination.

Discussion

Results from the SENZA-RCT provide level I evidence of the safety and efficacy of 10-kHz SCS in patients with CLBP from a variety of etiologies, including some who were surgery naive.[30] However, most patients in the SENZA-RCT and other large prospective trials of 10-kHz SCS in CLBP have reported a history of spine surgery and, thus, were assigned a diagnosis of FBSS.[10–13] FBSS pain is often multifactorial due to tissue manipulation, surgical complications, new or persistent neuropathic pain, and/or central somatic sensitization,[14] and, therefore, may overlap with the NSRBP pain etiology. Although the efficacy of 10-kHz SCS for treating surgery-naive back pain has been supported by smaller prospective case se-

TABLE 3. Summary of study-related SAEs

	No. of SAEs	No. of Pts w/ SAEs (%), n = 145	Action Taken/Comments
Implant site infection	2	2 (1.4)	IPGs were explanted & reimplanted when infection resolved.
Poor wound healing	1	1 (0.7)	Treated w/ device explant & primary closure.
Lethargy	1	1 (0.7)	Severe lethargy due to narcotic use, resulting in extended hospital stay; symptoms resolved w/o further sequelae.
Osteomyelitis	1	1 (0.7)	Developed osteomyelitis as a complication of the trial & did not go on to receive a permanent implant.
Total	5	5 (3.4)	

ries and the outcomes of larger subcohort studies,[10,11,17,31] this is the first RCT conducted in a large NSRBP patient population.

The results presented here show profound improvements for patients with NSRBP who received 10-kHz SCS in addition to CMM compared with those who received CMM alone. The primary endpoint was met and strongly favored the addition of 10-kHz SCS to CMM, as more than 80% of patients qualified as responders with pain relief of ≥ 50%. This response rate is comparable with that reported in large studies conducted primarily or entirely within the FBSS patient population, including the pivotal SENZA-RCT.[10,11,15] The responder rate for the original 10-kHz SCS arm and the crossover group in our study is also similar to the 75% responder rate reported in the small pilot study.[17] Finally, our results are comparable with real-world evidence from a large retrospective study (n = 844) in Europe and the United States that found a 12-month responder rate of 77.6% in patients with chronic back and leg pain,[32] further demonstrating the stability of the results across several geographic regions and different populations of patients with CLBP.

The secondary endpoints, which assessed measures of function, quality of life, patient satisfaction, and opioid analgesic usage, were all significantly improved with 10-kHz SCS relative to CMM alone. The mean ODI score decreased by 24.2 points after 3 months in the stimulation arm, and was 22.7 points lower after 12 months, more than double the MCID of 10 points.[24,25,29] The proportion of patients in the 10-kHz SCS arm who had ODI score decreases exceeding 10 points (ODI responders) was 78.5%. The mean pain intensity in patients who received SCS decreased 5.4 cm (72.0%), which is more than twofold the MCID of 2 cm.[33] Compared with previous studies in the FBSS population, the concordance of these results in patients with NSRBP supports the comparable efficacy of therapeutic treatment with 10-kHz SCS.

Despite no specified opioid weaning protocol, usage in this study declined by 45.8% on average in patients who received SCS treatment, while it increased among patients who received CMM alone. The changes were significant, even with the high variation in prescribed opioid dosages across patients in both groups. Opioid-sparing effects have been seen in many other studies of 10-kHz SCS.[15] This is significant because opioid-related AEs negatively impact a patient's quality of life with little evidence of long-term efficacy, and high doses of opioids expose patients to the more serious risks of misuse and overdose.[34]

In the current RCT, study-related AE rates were similar to those reported in the literature, including the SENZA-RCT which had a study-related AE rate of 27.7%.[10] The most common related AE was IPG site pain (4.8%), comparable with 5% to 10% reported in the literature.[35–37] The 3.4% infection rate is also similar to reports in the literature.[36,38] There were no explantations due to loss of efficacy.

All outcomes were stable for the 12 months of follow-up in the 10-kHz SCS arm and patients who crossed over to the 10-kHz SCS therapy had comparable improvements postcrossover.

Limitations

This study is potentially limited by the lack of ability to blind between treatment groups, which could introduce bias into the results. However, this is a pragmatic, open-label study that is not designed to control for patient expectations or the placebo effect since these factors are present in the real-world treatment of NSRBP.[7]

Several measures have been taken to minimize potential study bias, including the participation of outside medical experts in the design of the study and the utilization of independent physician investigators for patient selection, data collection, and oversight of study conduct at their respective sites. An independent statistician provided the interim analysis and evaluation of primary and secondary endpoints per a prespecified statistical analysis plan. In addition, the primary endpoint was reported for the ITT population, while secondary outcomes were reported for the PP population. Attrition, which is the percentage of all randomized patients (ITT group) with reported outcomes, is an important measure of the overall conduct of any RCT, with a follow-up rate of < 80% associated with a lower level of evidence.[39,40] In this study, 94% and 92% of the randomized patients had reported outcomes at 3 and 6 months, respectively.

These results have strong applicability to real-world spine specialists and the pain management community given that, other than the requirement that patients meet the definition of NSRBP, the inclusion criteria were based on requirements for SCS implantation in the standard clinical setting. Also, the control treatment (CMM) represents the only currently available therapy options for patients with NSRBP. One may argue that the control group is flawed in that CMM has already been tried and failed, but the purpose of this study was to quantify the benefits of adding 10-kHz SCS to the established standard of care for these patients. The fact that CMM was not precisely prescribed by the protocol may be considered a limitation since it is dependent on the best practice at each site, but it also allowed for continuation of individualized care. This individualized care may have helped ameliorate the potential confounding effect on the patient-reported outcomes related to potential disappointment over being randomized to receive care they were already receiving.

The pragmatic inclusion criteria and lack of a standardized CMM therapy strengthen the external validity of the study, for clinicians making patient care decisions and for medical payers who do not currently reimburse for SCS therapy in this population; hopefully, this provides evidence supporting expanded access to SCS therapy for patients with NSRBP. The SCS-implanted cohort will be followed observationally for 24 months in order to corroborate long-term data obtained in a small feasibility study[16] that demonstrated durable efficacy and benefit in this population. Moreover, successful experience with salvaging failed traditional SCS implants by replacing them with 10 kHz implants[41,42] has suggested that 10-kHz SCS may be more effective than traditional SCS in the long term.

It bears repeating that each patient was examined and worked up by a spinal surgeon who confirmed that they were not candidates for direct operative intervention.

These patients were evaluated and ruled out for spinal tumor, fracture, infection, instability, significant compressive disease, or spondylosis amenable to surgical correction that would likely lead to significant improvement in their condition. Each patient had also exhausted all available appropriate nonoperative medical management including physical therapeutics, injection therapy, and trials of oral medications for their intractable low-back pain. The long interval of time between diagnosis and enrollment in the study seen for most patients (median of approximately 8 years in treatment groups and ≥ 50 years on the high end) demonstrates the refractory nature of their pain and the need for safe and effective treatments.

Conclusions

The current study has demonstrated that the addition of 10-kHz SCS to CMM resulted in profound improvements in pain relief, function, quality of life, and awareness of positive change, as well as reduction in daily opioid use, 12 months postimplantation. The quality-of-life improvement achieved is more than double the MCID, while maintaining a good safety profile and with the added advantage of being a completely reversable therapy.

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Supplemental material is available with the online version of the article.

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