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Multicolumn spinal cord stimulation for predominant back pain in failed back surgery syndrome patients: a multicenter randomized controlled trial

Philippe Rigoard[a,b,c,*], Surajit Basu[d], Mehul Desai[e,f], Rod Taylor[g], Lieven Annemans[h], Ye Tan[i], Mary Jo Johnson[i], Carine Van den Abeele[j], PROMISE Study Group, Richard North[k,l]

Abstract

Despite optimal medical management (OMM), low back pain (LBP) can be disabling, particularly after spinal surgery. Spinal cord stimulation (SCS) is effective in reducing neuropathic leg pain; however, evidence is limited for LBP. This prospective, open-label, parallel-group trial randomized (1:1) failed back surgery syndrome (FBSS) patients with predominant LBP to SCS plus OMM (SCS group) or OMM alone (OMM group) at 28 sites in Europe and the Americas. If trial stimulation was successful, a multicolumn SCS system was implanted. Outcomes were assessed at baseline (before randomization) and at 1, 3, 6, and 12 months after randomization. Patients could change treatment groups at 6 months. The primary outcome was the proportion of patients with ≥50% reduction in LBP (responder) at 6 months. Secondary outcomes included change in pain intensity, functional disability, and health-related quality of life (HRQoL). The results are posted at ClinicalTrials.gov under registration number NCT01697358. In the intent-to-treat analysis, there were more responders in the SCS group than in the OMM group (13.6%, 15/110 vs 4.6%, 5/108, difference 9% with 95% confidence interval 0.6%-17.5%, $P = 0.036$) at 6 months. The SCS group improved in all secondary outcomes compared with the OMM group. The OMM group only improved in HRQoL. In the SCS group, 17.6% (18/102) experienced SCS-related adverse events through 6 months, with 11.8% (12/102) requiring surgical reintervention. Adding multicolumn SCS to OMM improved pain relief, HRQoL, and function in a traditionally difficult-to-treat population of failed back surgery syndrome patients with predominant LBP. Improvements were sustained at 12 and 24 months.

Keywords: Spinal cord stimulation, Surgical leads, Failed back surgery syndrome, Randomized controlled trial, Chronic low back pain, Predominant back pain

1. Introduction

Spinal pathologies and low back pain (LBP) represent a major public health issue and impose a considerable financial burden on the society.[2] Low back pain affects 60% to 80% of the population at some point in life,[13,15] and pharmacological treatments can be suboptimal.[4,11]

A substantial fraction of patients who undergo spinal surgery develop new or persistent back and/or leg pain postoperatively.[4,19,20,23] This chronic condition is described as failed back surgery syndrome (FBSS) or postlaminectomy syndrome and remains difficult to treat with conventional medical management alone.[8]

Spinal cord stimulation (SCS) for pain control has been available for 50 years. It is delivered through electrodes placed in the dorsal epidural space to produce paresthesia in the painful area. Several systematic reviews of the impact of SCS in chronic back and leg pain and FBSS have been published.[16,31–33] The systematic review by Taylor et al. in 2014 identified 74 included SCS studies (in 3025 patients) of which only 4 studies (in 104 patients) were in the population with predominant LBP; the remainder were in predominant leg pain (9 studies), mixed back and leg pain (22 studies), or unclassifiable (39 studies). There was evidence of a higher level of pain relief pooled across studies in individuals with predominant back pain after SCS (mean 86% pain relief, 95% confidence interval [CI]: 75%-96%) compared with studies in those with predominant leg pain (mean 53% pain relief, 95% CI: 39%-68%), but the number of studies analyzed was small, and there was no significant association ($P = 0.49$) between the level of pain relief and the location of pain in univariable meta-regression. Furthermore, these 4 studies in predominant LBP were all case series and therefore low in the hierarchy of evidence. The authors recommended randomized controlled trials (RCTs) to confirm the effectiveness and cost-effectiveness of SCS in the population with predominant LBP that included important measurements beyond pain relief including level of physical disability and health-related quality of life (HRQoL). Although SCS is an established and effective treatment in FBSS for predominant radicular pain,[18,24,31] LBP has been difficult to treat with traditional SCS. Initial reports on the use of SCS with a multicolumn lead (electrode array) have shown promising results.[27]

PROMISE was designed to address this gap in LBP evidence. It is an international RCT of SCS in a population of exclusively predominant LBP FBSS patients to compare the clinical effectiveness of SCS with a multicolumn lead combined with optimal medical management (OMM) to OMM alone.

2. Methods

The PROMISE trial was conducted and reported in accordance with the Consolidated Standards of Reporting Trials guidelines.[22] The study design, previously published,[28] is summarized below.

2.1. Study design

PROMISE was a multicentre, prospective, randomized, open-label, parallel-group, controlled trial conducted at 28 investigational sites in Belgium, Canada, Colombia, France, Germany, the Netherlands, Spain, the United Kingdom, and the United States.

The study was conducted in accordance with ISO 14155, and ethics committee/institutional review board approval was obtained at each site. Surgeons at each site were required to have experience implanting a minimum of 6 multicolumn surgical leads before study participation.

2.2. Patients

Failed back surgery syndrome patients, identified through standard clinical practice at each site (eg, call logs, chart reviews, scheduled visits, and referrals), were evaluated systematically for study eligibility and provided consent before enrollment. Study patients had an FBSS diagnosis, no indication for further spine surgery, an average LBP score of $\geq$5 on the 7-day pain diary completed twice daily (morning and evening) at home using the Numeric Pain Rating Scale (NPRS), an average leg pain less than their mean back pain, and were candidates for SCS using the studied surgical lead.

The initial pain diary was completed after enrollment within 2 weeks before the randomization visit. Patients were not informed of the success criteria, and those who did not meet the pain inclusion criteria were discontinued from the study.

2.3. Randomisation and masking

Patients were randomly allocated (1:1 ratio) to SCS + OMM (SCS group) or OMM alone (OMM group) using random, permuted blocks of 4 and 2 stratified by investigational site. To maintain allocation concealment, randomization assignments were provided using an electronic data management system. Due to the nature of the treatments, the treating physicians and patients could not be blinded to the treatment group.

2.4. Procedures

Given the lack of international guidance, an OMM guideline was developed by the PROMISE Trial Steering Committee (TSC) to standardize practice in the study. An individual OMM treatment plan was developed for each patient and optimized at each visit. Optimal medical management could include treatments ranging from noninvasive treatments such as acupuncture, psychological/behavioural therapy, and physiotherapy to invasive treatments such as spinal injections/blocks, epidural adhesiolysis, and neurotomies.

Patients randomized to SCS underwent trial stimulation with a surgical lead or percutaneous leads, based on the standard practices used at the site. Trial success was defined as a subject having adequate LBP relief with usual activity and appropriate analgesia in the context of postoperative pain (thoracic laminectomy in particular, when applicable), as assessed by the investigator. If the trial was successful, a permanent SCS system was implanted using the multicolumn surgical lead (Specify 5-6-5; Medtronic) and neurostimulator (Models 37701, 37702, 37712, 37713, 37714, 97702, 97713, and 97714; Medtronic), according to usual practice at the site. Outcomes were assessed at baseline (before randomization) and at 1, 3, 6, 12, and 24 months after randomisation. After 6 months, patients could change treatment groups.

2.5. Outcomes

The primary analysis was the proportion of responders in each group. The primary outcome was success or failure, and success

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

The PROMISE Study Group: *Marc Deruytter, Johan Vangeneugden, Vincent Galan, Armando Villareal, Frank van Eijs, Joseph Buwembo, David Noriega, Sanjay Bhatia, Eric Tallarico, Jean-Michel Remacle, Stana Bojanic, To-Nhu Vu, Christian Raftopoulos, Santiago Jaramillo, Marcus Eif, Carlos Yepes, Adriana Lopez, Tony Van Havenbergh, Timothy Houden, Candice Burnette, Bart Edmiston, Neel Mehta, Guillermo García March, Shivanand P. Lad, and Julie Pilitsis.*

Department of Neurosurgery, AZ Delta Hospital, Roeselare, Belgium (M Deruytter, MD); Department of Neurosurgery, Sint Maarten General Hospital, Duffel, Belgium (J Vangeneugden, MD); Pain Care LLC, Stockbridge, GA, USA (V Galan, MD); University of Rochester, Rochester, NY, USA (A Villareal, MD); Department of Pain Management, Elisabeth Tweesteden Hospital, Tilburg, the Netherlands (F van Eijs, MD, PhD); Department of Neurosurgery, Regina General Hospital, Regina, SK, Canada (J Buwembo, MD); Department of Traumatology & Orthopedic surgery, Valladolid University Hospital, Valladolid, Spain (D Noriega, MD); West Virginia University Pain Management Center, Morgantown WV, USA (S Bhatia, MCh); New York Spine and Wellness Center, North Syracuse, NY, USA (E Tallarico, MD); Department of Neurosurgery, La Citadelle Regional Hospital, Liège, Belgium (J-M Remacle, MD); Department of Neurosurgery, John Radcliffe, Oxford University Hospitals NHS, Oxford, the United Kingdom (S Bojanic, MD); Wellspan Interventional Pain Management, York, PA, USA (T-N Vu, MD); Department of Neurosurgery, University Hospital St-Luc (UCL), Brussels, Belgium (C Raftopoulos, PhD); Department of Neurosurgery, Pablo Tobón Uribe Hospital, Medellin, Antioquia, Colombia (S Jaramillo, MD); Department of Neurosurgery, Görlitz Hospital, Görlitz, Germany (Marcus Eif, MD); Department of Neurosurgery, Las Américas Clinic, Medellin, Antioquia, Colombia (C Yepes, MD); San Vicente Foundation, Rionegro, Antioquia, Colombia (A Lopez, MD); Department of Neurosurgery, GZA - Sint Augustinus Hospital, Wilrijk, Belgium (T Van Havenbergh, MD); Utah Spine Care, Ogden, UT, USA (T Houden, MD); UT Physicians Richmond Bone and Joint, Sugar Land, TX, USA (C Burnette, MD); Ocean Springs Neuroscience Center, Ocean Springs, MS, USA (B Edmiston, MD); Weill Cornell Medicine, New York, NY, USA (N Mehta, MD); Department of Neurosurgery, University Hospital, Valencia, Spain (G García March, PhD); Department of Neurosurgery, Duke University, Durham, NC, USA (S. P. Lad, MD); and Department of Neurological Surgery, Albany Medical Center, Albany, NY, USA (Prof. J Pilitsis, MD).

[a] Department of Neurosurgery, Poitiers University Hospital, Poitiers, France, [b] PRISMATICS Lab, Faculty of Medicine, University of Poitiers, Poitiers, France, [c] UMR 3346, CNRS, P' Institute, Futuroscope, Poitiers, France, [d] Department of Neurosurgery, Nottingham University Hospital, Nottingham, United Kingdom, [e] International Spine, Pain and Performance Center, Washington, DC, United States, [f] George Washington University Medical Center, Washington, DC, United States, [g] Institute of Health Research, University of Exeter Medical School, Exeter, United Kingdom, [h] Interuniversity Centre for Health Economics Research, Ghent University, Brussels University, Ghent and Brussels, Belgium, [i] Department of Clinical Research, Medtronic, Minneapolis, MN, United States, [j] Department of Clinical Research, Medtronic International Trading Sàrl, Tolochenaz, Switzerland, [k] The Neuromodulation Foundation, Inc, Baltimore, MD, United States, [l] Department of Neurosurgery, Johns Hopkins University (retired), Baltimore, MD, United States

**Corresponding author. Address: Department of Neurosurgery, Poitiers University Hospital, CHU de Poitiers, Laboratoire PRISMATICS Bâtiment CCV Etage 0 2, rue de la Milétrie CS 90577 86000 Poitiers, France. Tel.: + 33(0) 5 49 44 32 23; fax: + 33(0) 5 49 44 32 18. E-mail address: philipperigoard@yahoo.fr (P. Rigoard).*

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was defined as ≥50% reduction in LBP. Secondary outcomes were back and leg pain intensity (NPRS), disability (Oswestry Disability Index [ODI][10]), and HRQoL (Short Form-36 [SF-36] Physical Component Score [PCS][35]).

Additional outcome measures included the ≥30% LBP responder rate, 2-point LBP responder rate, SF-36 Mental Component Score, EuroQoL-5D (EQ-5D-5L),[12] sleep (Pittsburgh Sleep Quality Index),[3] Patient Global Impression of Change (PGIC),[14] employment status, pain treatments, and patient satisfaction.

Adverse events (AEs) were reported and coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1. An independent clinical events committee adjudicated AEs.

There were 3 analysis sets: intent-to-treat (ITT), completers, and as-treated. The ITT analysis consisted of all patients according to the randomization allocation. Completers analysis consisted of patients according to the randomization allocation who contributed complete data sets. As-treated analysis consisted of patients' actual treatment at the analysis timepoint and complete data sets.

2.6. Statistical analysis

The primary hypothesis was that the proportion of LBP responders in the SCS group would be greater than that in the OMM group. A minimum sample of 212 was required to provide 90% power to detect a between-group difference of 20% in responder rates. The assumptions of between-group difference were based on results of the PROCESS RCT.[18] Sample size reestimation was conducted by an independent statistician when 140 patients reached 6 months of follow-up using Lan-DeMets with O'Brien-Fleming boundary methods. No adjustments to sample size resulted from this analysis.

For the primary and secondary objectives at 6 months, the primary analysis followed the ITT principle. In addition, completers and as-treated analyses were undertaken. The following analysis definitions were applied: ITT, between-group comparison based on random allocation of all patients; completers, between-group comparison based on random allocation of patients with complete data; and as-treated, between-group analysis based on the treatment received at 6 months and on patients with complete data. Patients with missing data were treated as nonresponders for the primary objective and no-change for secondary objectives for the ITT analysis. For additional outcome measures, the as-treated populations were used.

Responder rates were compared by a Z-test using an unpooled SD with continuity correction between the SCS and OMM groups. Linear regression models were used to assess secondary outcomes, comparing the baseline to follow-up score changes between the SCS and OMM groups, adjusting for baseline outcome scores. A treatment-by-site interaction term was tested in each model. If the interaction term approached significance (defined as <0.10), that term remained in the final model with the term for site. In addition, within-group comparisons to baseline were performed using a paired *t* test or a Wilcoxon signed rank test.

Given the extent of patient cross-over to SCS after 6 months, 12-month and 24-month analyses were limited to a within-group comparison in the SCS group using either a paired *t* test or a Wilcoxon signed rank test. In an exploratory post hoc analysis using univariate and multivariate logistic regression, demographic factors of age, sex, body mass index (BMI), region, duration of FBSS, number and type of prior spinal surgeries (fusion vs nonfusion), type of pain, and worker's compensation were analyzed.

A *P*-value of <0.05 was considered statistically significant. To maintain an overall type I error rate at 0.05, a fixed-sequence method for the multiplicity adjustment of hierarchical endpoints was used for the primary and secondary objectives. Analyses were prespecified in a detailed statistical analysis plan and performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC). A data monitoring committee was not used for this study, given that the TSC was providing oversight.

The study is posted at Clinicaltrials.gov under registration number NCT01697358.

2.7. Role of the funding source

Medtronic funded the study and was involved in the study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Study population

Patients were screened from January 8, 2013, through August 31, 2015, with the last patient enrolled on August 15, 2015, and the final patient visit on June 20, 2017. Of the 2858 FBSS patients screened, 1199 were considered as potential candidates, 548 (46%) opted not to participate, and 373 (31%) were excluded due to SCS and/or study contraindication(s). A total of 278 patients were enrolled, of which 218 were randomized, 110 to SCS with OMM and 108 to OMM alone. Patient disposition is provided in **Figure 1**.

Baseline characteristics and outcomes did not differ between groups (**Table 1**). Overall, randomized patients experienced FBSS symptoms for 6.7 years on average. Previous surgeries were 68.5% fusion (fusion or disk replacement) and 31.2% nonfusion (discectomy, laminectomy, laminotomy, foraminectomy, foraminotomy, and other). The majority had more than one surgery and were unable to work. Mean pain was predominant in the back (7.5/10) and moderate (5.3/10) in the leg(s). Pain seemed to be neuropathic in 84.4% of cases as indicated by the Neuropathic Pain questionnaire, Douleur Neuropathique 4 [DN4][1]. Most patients reported severe disability (mean ODI: 54.9) and low HRQoL (mean EQ-5D-5L index: 0.35). Mean BMI was 29.8 kg/m^2.

3.2. Temporary trial period

In the SCS group, 69.6% (71/102) of patients were trialed with the multicolumn surgical lead and 30.4% (31/102) with percutaneous leads. Of the 102 patients trialed, 82 (80.3%) continued to permanent system implant, with 52.4% (43/82) receiving a rechargeable system and 47.6% (39/82) a nonrechargeable system.

3.3. Permanent system

All patients received the multicolumn surgical lead and a compatible neurostimulator (model 97714, n = 49; 37702, n = 39; 97702, n = 27; 37714, n = 12; 97712, n = 4; 37713, n = 3; 97713, n = 3; 37712, n = 2; and 37701, n = 1). Eighty-two neurostimulators were implanted in the SCS + OMM patients and 58 neurostimulation systems were implanted in the OMM patients, 1 before the 6-month visit and the others after the 6-month visit.

3.4. Primary outcome at 6 months

In the ITT analysis, 15 SCS patients (13.6%) and 5 OMM patients (4.6%) achieved ≥50% LBP relief (risk difference 9% with 95% CI

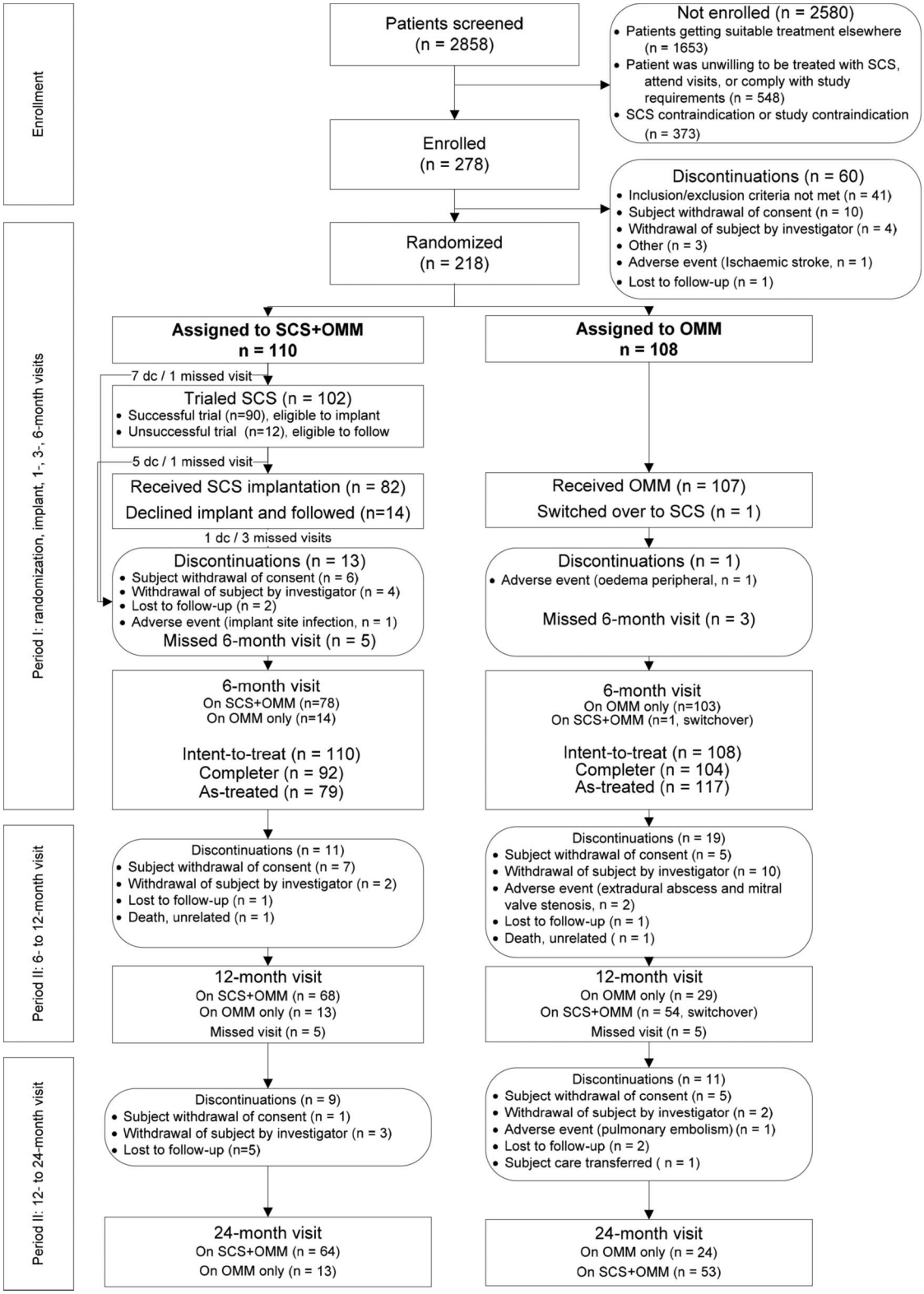


Figure 1. CONSORT diagram of patient flow. OMM, optimal medical management; SCS, spinal cord stimulation.

0.6%-17.5%, $P = 0.036$, **Table 2**). The primary objective was met. The SCS group responder rate ranged from 0% to 50% across sites.

In the completers analysis, the LBP responder rate in the SCS group was 16.3% and it was 4.8% ($P = 0.017$) in the OMM group. In the as-treated analysis, the LBP pain responder rate in the SCS group was 20.3% and it was 3.4% ($P = 0.001$) in the OMM group (**Table 2**).

The proportion of the as-treated SCS group reporting a clinically meaningful reduction in LBP of ≥30% was 39.2% compared with 12.0% in the OMM group. The proportion of SCS group patients with a ≥2-point LBP NPRS reduction was 43.0%

Table 1

Baseline demographics.

Variable	Total randomized	SCS + OMM	OMM
	N = 218	n = 110	n = 108
Age at consent (y): Mean (SD)	53.9 (11.5)	52.8 (12.5)	55.1 (10.2)
Sex: Female, n (%)	132 (60.6%)	68 (61.8%)	64 (59.3%)
Body mass index (BMI): Mean (SD)	29.8 (5.4)	30.0 (5.1)	29.7 (5.7)
Etiology of pain that led to original surgery, n (%)			
Herniated disk	109 (50.0%)	57 (51.8%)	52 (48.2%)
Other (combinations)	66 (30.3%)	33 (30.0%)	33 (30.6%)
Spondylolisthesis	17 (7.8%)	9 (8.2%)	8 (7.4%)
Unknown	17 (7.8%)	9 (8.2%)	8 (7.4%)
Spinal deformity	6 (2.8%)	2 (1.8%)	4 (3.7%)
Fracture	3 (1.4%)	0 (0%)	3 (2.8%)
Years since FBSS symptoms onset: Mean (SD)	6.7 (7.2)	6.4 (7.4)	7.0 (7.1)
Years since last surgery*: Mean (SD)	5.4 (5.9)	5.3 (6.2)	5.6 (5.5)
No. of previous spinal surgeries*: Mean (SD)	2.0 (1.2)	1.9 (1.2)	2.0 (1.3)
Unable to work, n (%)	111 (50.9%)	64 (58.2%)	47 (43.5%)
Neuropathic pain (DN4 ≥4), n (%)	184 (84.4%)	94 (85.5%)	90 (83.3%)
Low back pain NPRS: Mean (SD)	7.5 (1.2)	7.5 (1.2)	7.6 (1.2)
Leg pain NPRS: Mean (SD)	5.3 (2.0)	5.4 (1.9)	5.3 (2.1)
EQ-5D-5L index value	0.35 (0.26)	0.34 (0.27)	0.36 (0.24)
ODI: Mean (SD)	54.9 (14.4)	55.0 (14.6)	54.8 (14.4)

* All patients had at least one previous spinal surgery, either fusion (fusion or disk replacement) or nonfusion (discectomy, laminectomy, laminotomy, foramenectomy, foraminotomy, or other).
FBSS, failed back surgery syndrome; NPRS, Numeric Pain Rating Scale; ODI, Oswestry Disability Index; OMM, optimal medical management; SCS, spinal cord stimulation.

compared with 11.1% in OMM patients. (Table S1, available at http://links.lww.com/PAIN/A751).

The post hoc exploratory regression analysis identified that BMI and treatment allocation were the only predictors of the primary outcome for both groups.

3.5. Secondary outcomes at 6 months

Secondary endpoint ITT, completers, and as-treated analyses are reported in **Table 3**.

In the as-treated analysis, mean back and leg pain intensity in the SCS group were reduced 2.0 points, from 7.5 to 5.4 ($P < 0.001$), and 1.6 points, from 5.2 to 3.7 ($P < 0.001$), respectively, and were unchanged in the OMM group (**Table 3** and **Figs. 2 and 3**). The leg pain responder rate in the SCS group was 40.5% and 8.5% in the OMM group (Table S1, available at http://links.lww.com/PAIN/A751). Mean ODI score decreased from 55.9 to 43.9 in the SCS group ($P < 0.001$) and was unchanged in the OMM group (from 54.4 to 53.2) (**Table 3**). The proportion of patients in the "crippled"/"bedbound" categories was reduced from 40.5% to 13.9% in the SCS group and from 33.4% to 28.2% in the OMM group (**Fig. 4**). For HRQoL, mean SF-36 PCS scores improved from 24.08 to 31.58 ($P < 0.001$) in the SCS group and were unchanged in the OMM group (**Table 3**).

3.6. Additional results at 6 months

Additional outcomes were evaluated at 6 months using the as-treated data set. All, except work status and SF-36 Mental Component Score, improved in the SCS group and were unchanged in the OMM group. (Table S2, available at http://links.lww.com/PAIN/A751). In the SCS group, mean EQ-5D-5L index value increased from 0.31 to 0.49, and the Pittsburgh Sleep Quality Index improved from 13.1 to 10.8. A significant favorable PGIC improvement ("moderately," "better," or "a great deal better") was reported in 59.0% of SCS group patients compared with 10.3% in the OMM group. Satisfaction was high with 82.1% of SCS patients stating they were "somewhat" or "very satisfied" with the therapy, compared to 53.9% in the OMM group.

The number of OMM treatments received differed between the 2 treatment groups; 3.8% (3/79) of SCS subjects used a total of 3 invasive treatments between baseline and 6 months compared with 24.8% (29/117) of OMM subjects who used a total of 69 invasive treatments. For noninvasive treatments, 30.4% (24/79) of SCS subjects used a total of 431 noninvasive treatments compared with

Table 2

Primary outcome: LBP responders at 6 months.

Analysis	SCS + OMM responders			OMM responders			Between-group risk difference (95% CI)	Between-group difference, *P*
	#	n	%	#	n	%		
ITT	15	110	13.6	5	108	4.6	9% (0.6%-17.5%)	0.036
Completers	15	92	16.3	5	104	4.8	11.5% (1.9%-21.1%)	0.017
As-treated	16	79	20.3	4	117	3.4	16.8% (6.3%-27.3%)	0.001

CI, confidence interval; ITT, intent-to-treat; LBP, low back pain; OMM, optimal medical management; SCS, spinal cord stimulation.

Table 3

Secondary outcomes: NPRS, ODI, and HRQoL at 6 months.

Secondary outcomes	SCS + OMM				OMM				Between-group difference, (95% CI)	Between group, *P*
	Baseline	6-mo	Change from baseline	Within group, *P*	Baseline	6-mo	Change from baseline	Within group, *P*		
Low back pain NPRS mean (SD)										
ITT	7.5 (1.2)	6.0 (2.1)	1.4 (1.9)	<0.001	7.6 (1.2)	7.2 (1.9)	0.3 (1.7)	0.399	1.1 (0.6-1.6)	<0.001
Completers	7.5 (1.2)	5.8 (2.1)	1.7 (2.0)	<0.001	7.6 (1.2)	7.2 (1.9)	0.4 (1.7)	0.399	1.3 (0.8-1.9)	<0.001
As-treated	7.5 (1.2)	5.4 (2.1)	2.0 (1.9)	<0.001	7.5 (1.2)	7.3 (1.8)	0.3 (1.6)	0.507	1.7 (1.2-2.2)	<0.001
Leg pain NPRS mean (SD)										
ITT	5.4 (1.9)	4.2 (2.4)	1.2 (2.1)	<0.001	5.3 (2.1)	5.4 (2.4)	−0.1 (2.4)	0.437	1.3 (0.7-1.9)	<0.001
Completers	5.3 (1.8)	3.9 (2.4)	1.4 (2.2)	<0.001	5.2 (2.1)	5.3 (2.5)	−0.1 (2.4)	0.437	1.5 (0.9-2.2)	<0.001
As-treated	5.2 (1.9)	3.7 (2.4)	1.6 (2.3)	<0.001	5.3 (2.0)	5.4 (2.4)	−0.0 (2.3)	0.684	1.6 (0.9-2.3)	<0.001
ODI mean (SD)										
ITT	55.0 (14.6)	46.9 (17.9)	8.1 (14.7)	<0.001	54.8 (14.4)	53.1 (17.1)	1.8 (14.3)	0.093	6.3 (2.5-10.2)	<0.001
Completers	55.0 (14.2)	45.3 (17.7)	9.7 (15.6)	<0.001	55.0 (14.3)	53.2 (17.1)	1.8 (14.6)	0.093	7.9 (3.6-12.1)	<0.001
As-treated	55.9 (14.6)	43.9 (18.4)	12.0 (16.1)	<0.001	54.4 (14.0)	53.2 (16.4)	1.1 (13.5)	0.192	10.9 (6.7-15.1)	<0.001
HRQoL, SF-36 PCS mean (SD)										
ITT	24.55 (7.13)	29.82 (9.78)	5.27 (8.28)	<0.001	24.72 (6.70)	26.06 (6.59)	1.34 (6.28)	0.028	3.9 (2.0-5.9)	<0.001
Completers	24.06 (6.80)	30.35 (9.98)	6.30 (8.69)	<0.001	24.61 (6.78)	26.00 (6.67)	1.39 (6.39)	0.028	4.9 (2.8-7.0)	<0.001
As-treated	24.08 (6.73)	31.58 (10.04)	7.50 (8.72)	<0.001	24.53 (6.83)	25.66 (6.60)	1.12 (6.17)	0.071	6.4 (4.3-8.5)	<0.001

CI, confidence interval; HRQoL, health-related quality of life; ITT, intent-to-treat; NPRS, Numeric Pain Rating Scale; ODI, Oswestry Disability Index; OMM, optimal medical management; PCS, Physical Component Score; SCS, spinal cord stimulation.

47.9% (56/117) of OMM subjects who used a total of 1622 treatments. Scheduled study visits were at 1, 3, 6, 12, and 24 months after randomization. Outside these regularly scheduled visits, 60.8% (48/79) of SCS subjects in the as-treated analysis had a total of 401 nontreatment consultations compared with 49.6% (58/117) of OMM subjects who had a total of 246 consultations (Table S3, Fig. S1, available at http://links.lww.com/PAIN/A751).

When taking all 3 types of contacts (invasive, noninvasive, and nontreatment consultations) into consideration, the OMM subjects had more than twice as many interactions with a health care provider as the SCS subjects.

The proportion of patients taking pain medication decreased or remained unchanged in the SCS group and increased in the OMM group, except for anxiolytics, which increased in both groups. In the SCS group, pain medication changes were associated with "pain level improvement" in 46.8% of patients compared to 17.9% in the OMM group. Medication changes due to "side effects" were higher in the OMM group (20.5%) than in the SCS group (2.5%) (Tables S4 and S5, available at http://links.lww.com/PAIN/A751). Mean baseline morphine milligram equivalents (MME) dosage in the SCS group was 59.5 and 57.5 in the OMM group. At 6 months, there was a statistically significant difference in MME between groups ($P = 0.031$) with mean MME unchanged (58.5) in the SCS group and increased (64.8) in the OMM group. (Table S2, available at http://links.lww.com/PAIN/A751).

Spinal cord stimulation programming information is provided in Tables S6 and S7 and Fig. S2, available at http://links.lww.com/PAIN/A751.

At 6 months, 2.4% (2/83) of SCS-implanted patients opted to cease SCS therapy, whereas 72.6% (77/106) of OMM patients requested to crossover to SCS (Table S8, available at http://links.lww.com/PAIN/A751).

3.7. Twelve-month outcomes

Analysis was performed on patients reaching 12 months, those continuing SCS from Period I (SCS-SCS) and OMM subjects moving to SCS in Period II (OMM-SCS). Of the 61.8% (68/110) continuing SCS and reporting 12-month data, 26.5% (18/68) achieved ≥50% reduction in LBP (Table S9, Fig. S3, available at http://links.lww.com/PAIN/A751). Mean (SD) LBP improvement in patients continuing SCS at 12 months was 2.3 (2.2) points. In SCS-SCS patients with baseline and 12-month data (n = 66), mean (SD) improvements were seen in ODI 10.7 (18.6), EQ-5D-5L 0.17 (0.30), and SF-36 PCS 6.92 (8.30), all with $P < 0.001$.

3.8. Twenty-four-month outcomes

Of the 57.3% (63/110) continuing SCS (SCS-SCS) and reporting 24-month data, 20.6% (13/63) achieved ≥50% reduction in LBP (Table S9, Fig. S3, available at http://links.lww.com/PAIN/A751). Mean (SD) LBP improvement was 2.2 (2.0) points. Mean (SD) improvements were seen in ODI 9.4 (15.2), EQ-5D-5L 0.18 (0.29), and SF-36 PCS 6.45 (8.71), all with $P < 0.001$.

3.9. Adverse events

In the SCS group, 17.6% (18/102) of trialed patients experienced SCS-related AEs during the period from randomization through 6 months (**Table 4**). Among these, 11.8% (12/102) required surgical intervention to treat the event. The most frequent SCS-related AE was implant site infection (6.9%), in which 7 patients experienced 8 implant site infection events. Infections were associated with longer temporary trial duration and resulted in a protocol change to limit trial duration to 10 days or fewer.

Among all trialed patients regardless of randomization assignment, the SCS-related AE analysis at 24 months concluded that the overall infection rate was 5% (9/174), after combining infections that occurred within 90 days of initial lead implant (implant site infection, extradural abscess, and implant cellulitis) (Table S10, available at http://links.lww.com/PAIN/A751). The patient with extradural abscess also experienced hematoma and monoparesis, which resolved with sequela of paresis at the time of study exit after lead explant. The most frequent non–SCS-related AEs were falls and adverse drug reactions (Table S11, available at http://links.lww.com/PAIN/A751).

4. Discussion

The PROMISE study shows that the addition of SCS to OMM for patients with FBSS with predominant LBP was superior on back

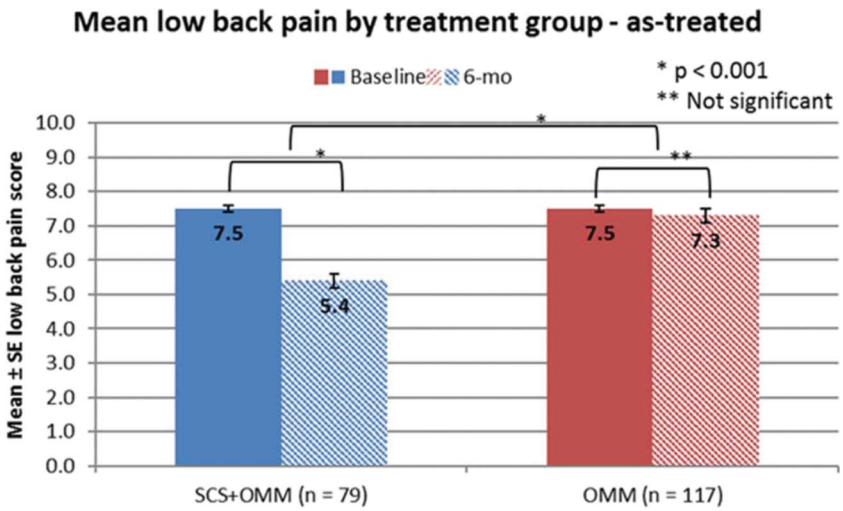


Figure 2. Low back pain intensity, as-treated. OMM, optimal medical management; SCS, spinal cord stimulation.

and leg pain, HRQoL, function, PGIC, and satisfaction compared to OMM alone. These improvements observed at 6 months with SCS were sustained at 12 and 24 months. The safety profile of SCS is in line with the literature. Despite more patients in the OMM group using invasive/semiinterventional treatments (24.8% of OMM subjects compared with 3.8% of SCS subjects), non-invasive treatments (47.9% compared with 30.4%), and increasing medications during the 6-month comparative phase, the OMM group did not show a statistically or clinically meaningful change in back or leg pain NPRS or function. The SCS group, however, showed both a statistically and clinically meaningful reduction in pain and improvement in function in this difficult-to-treat population, with stable/reduced medication intake.

In this multicenter study, the magnitude of reduction in pain and 50% response is lower than that reported in studies with the same lead,[26,27,29] other leads,[25] or alternative frequencies of SCS stimulation.[17] In studies with the same lead, an observational single-center study of 11 carefully selected FBSS patients reported a mean VAS back pain score decrease from 7.8 baseline to 1.5 at 6 months.[27] A prospective, three-center study of 76 consecutive patients reported that 42.1% of patients obtained at least 50% improvement of the back pain VAS score.[29] A larger single-center prospective observational study of 62 patients reported mean VAS change from 9 preoperatively to 5 at 36 months.[26] We believe that the modest pain effects with SCS seen in the study may reflect the difficult-to-treat population in this trial.

Although recent RCTs reaffirmed the benefits of SCS, in contrast to PROMISE, they did not specifically enroll patients with predominant LBP FBSS.[7,17] The Senza study enrolled subjects with back pain and leg pain ≥5.[17] The SUNBURST study enrolled patients with a mix of chronic trunk and/or limb pain with inclusion criteria of VAS pain scores ≥60.[30]

Moreover, the PROMISE patient population is more functionally impaired than in other studies. First, 36% of patients rated themselves as "crippled" compared with 20% in the SENZA study. Second, patients came into the study with a long history of back pain, functional disability, and poor HRQoL. Third, their average BMI was 29.8 kg/m^2 (ie, borderline obese), which was

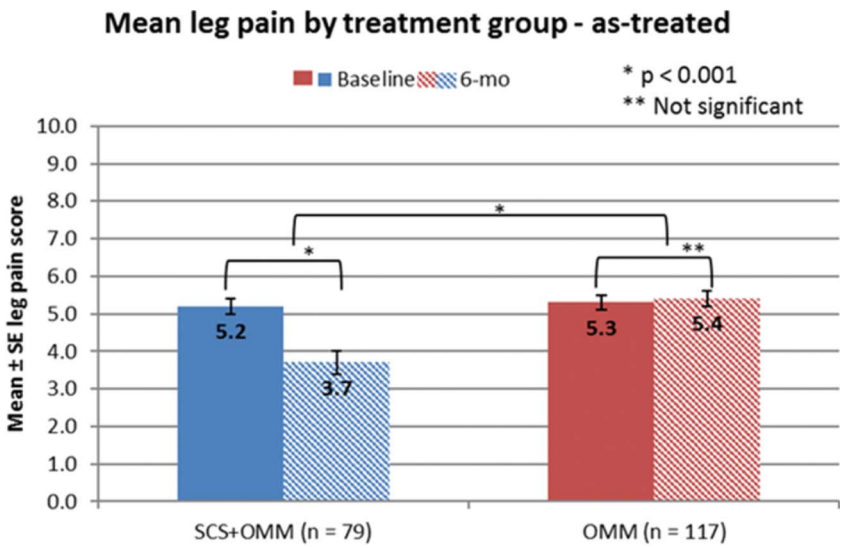
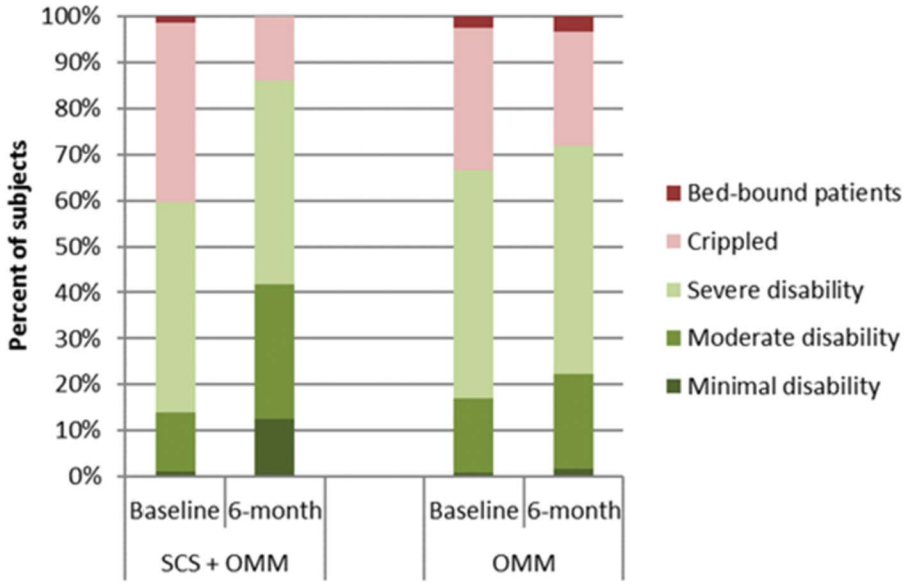


Figure 3. Leg pain intensity, as-treated. OMM, optimal medical management; SCS, spinal cord stimulation.



ODI categories	ODI scores	SCS + OMM				OMM			
		Baseline		6-month		Baseline		6-month	
		n	%	n	%	n	%	n	%
Minimal disability	[0, 20]	1	1.3%	10	12.7%	1	0.9%	2	1.7%
Moderate disability	(20, 40]	10	12.7%	23	29.1%	19	16.2%	24	20.5%
Severe disability	(40, 60]	36	45.6%	35	44.3%	58	49.6%	58	49.6%
Crippled	(60, 80]	31	39.2%	11	13.9%	36	30.8%	29	24.8%
Bed-bound patients	(80, 100]	1	1.3%	0	0.0%	3	2.6%	4	3.4%
Total		79	100.0%	79	100.0%	117	100.0%	117	100.0%

Figure 4. Oswestry Disability Index, as-treated. ODI, Oswestry Disability Index; OMM, optimal medical management; SCS, spinal cord stimulation.

shown to be a statistically significant prognostic factor for the primary outcome (higher BMI correlated with a lower level of response to SCS and OMM).

It is important to note that despite relatively small improvement in pain relief, the gains in HRQoL, function, and patient satisfaction with SCS reported by patients in this study are comparable with the those reported in the literature.[7,17,18,24,25] The disproportionately better improvements in function, HRQoL, PGIC, and satisfaction compared with pain reduction point not only to the importance of using HRQoL and function in assessing

Table 4

Spinal cord stimulation–related adverse events, randomization to 6-month visit.

CEC[a]-adjudicated etiology	MedDRA preferred term	No. of serious events	No. of events	No. of patients with events	Proportion of patients with event (n = 102[b])	No. of patients with surgical intervention
Device	Device stimulation issue	2	2	2	2.0%	2
	Paresthesia	0	2	2	2.0%	2
Human Factors	Device deployment issue	0	2	2	2.0%	2
	Device battery issue	0	1	1	1.0%	1
Programming/stimulation	Back pain	1	1	1	1.0%	0
Surgery/anesthesia	Implant site infection	7	8	7	6.9%	5
	Implant site cellulitis	0	1	1	1.0%	0
	Implant site pain	1	1	1	1.0%	1
	Pelvic pain	0	1	1	1.0%	0
	Pulmonary oedema	1	1	1	1.0%	0
	Urinary tract infection	1	1	1	1.0%	0
Total		13	21	18	17.6%	12

[a] CEC, Clinical Events Committee.
[b] Denominator (n = 102) is the number of patients who underwent a screening test.

therapy benefits[6] in a population suffering from chronic LBP, but also to the potential limitations of standard pain measures in this population.[5] Chronic LBP may have a mechanical component that is more susceptible to fluctuation based on activity.[34]

This trial has several strengths. First, patients were systematically selected and enrolled consecutively at trial centers across multiple geographies, which increases the generalizability of the study results. Second, sites were asked to develop an individual patient OMM treatment plan for all patients and review it at each patient visit to ensure OMM was optimized and the comparator was meaningful. The TSC authored OMM guidance for the study investigators based on an understanding of the current literature to define the OMM comparator as precisely and extensively as possible.[7] Third, outcomes were selected based on those endorsed by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)[9] and International Consortium for Health Outcomes Measurement.[6] The primary outcome was based on a 7-day, twice-daily paper pain diary and questionnaires that were completed by patients using a secure electronic tablet to reduce assessor bias. The use of pain intensity as the primary outcome in trials of chronic back pain has recently been criticized, and it has been recommended instead that studies should focus on the domains of physical functioning and HRQoL.[9,34] The results of this trial support the assertion that the traditional metric of ≥50% pain relief alone may fail to capture the value of improvements in disability and HRQoL. By incorporating secondary and additional outcomes, the PROMISE study was able to comprehensively evaluate therapy benefits.

This study has some limitations. Studies of "conventional" SCS are challenging to conduct in a double-blind fashion due to the implant procedure, the patient programmer, and the perceptible paresthesia experienced by subjects. The lack of blinding makes assessments susceptible to assessment bias and placebo and nocebo effects. The study used "conventional" SCS frequencies and waveforms. Although preoperative imaging (to define the level of the conus medullaris and guide lead implantation), intraoperative paresthesia mapping (to guide electrophysiological midline placement in awake patients), postoperative x-ray (to document lead position), postoperative algorithmic programming, and quantitative documentation of paresthesia coverage were all encouraged, the application of those was left to the discretion of the implanter and the center, and they were implemented and documented variably and pragmatically. Because the protocol did not include collection of imaging data and the study did not standardize implantation and programming practices across sites, it was not possible to determine whether lead placement and programming were optimized at some sites. This could, at least partially, explain the substantial variability of SCS responders across the sites, and these practices should be considered for further optimization of the therapy. The study population had a high BMI, which may compromise technically satisfactory SCS electrode placement not only because the surgical exposure is deeper, but also because it is more difficult to position a patient safely and comfortably under awake anesthesia in a prone position for paresthesia mapping.

The results of this study support the fact that multicolumn SCS may be considered for FBSS patients suffering from chronic predominant LBP. In recent years, alternative waveforms and delivery of higher energy[21,34] have emerged and show promising outcomes. Future studies are needed to explore methods for optimizing intraspinal neuroanatomical targeting (which technically rely on lead design, implantation parameters, and lead programming) and the use of these alternative waveforms/higher energy options (which depend on the pulse generator) as 2 complementary methods to increase SCS efficacy.

In conclusion, in this international multicenter RCT, adding SCS with a multicolumn lead to OMM provided statistically significant improvements in pain relief, HRQoL, and function compared with OMM alone in a traditionally difficult-to-treat FBSS patient population with predominant LBP. These improvements were sustained in the SCS group at 12 and 24 months.

Conflict of interest statement

L. Annemans has received grants from Medtronic. S. Basu has received funds to conduct the study and the associated hospital has received Medtronic equipment and hardware from Medtronic. S. Bojanic has received grants from Medtronic. J. Buwembo has received nonfinancial support from Medtronic. M. Desai has received personal fees from Medtronic and Halyard Health, and stock options from dorsaVi, SmartImplantSystems, and MedicalWearables Solutions. M. Eif has received personal fees from Medtronic. N. Mehta has received grants and personal fees from Nevro and Boston Scientific and grants from Medtronic. D. Noriega has received teaching fees from Vexim SAS and SPineart. R. North has received charitable grants from Abbott, Boston Scientific, Medtronic, Nevro, Stimwave, and Algostim/Nuvectra, personal fees from AlgoStim/Nuvectra, and has patents with royalties paid by Abbott and Nuvectra. J. Pilitsis has received grants and other consultant support from Medtronic, Boston Scientific, Abbott, Nevro, Jazz Pharmaceuticals, GE Global Research, Centauri, Karuna, and the NIH. J.-M. Remacle has received scientific support from Medtronic and personal fees from Depuy. P. Rigoard has received grants, personal fees, and nonfinancial support from Medtronic, Abbott, and Boston Scientific. R. Taylor has received personal fees and research consultancy fees from Medtronic. F. van Eijs has received personal fees from Medtronic. T. Van Havenbergh has received grants from Medtronic. A. Villareal has received grants and personal fees from Medtronic, grants from Boston Scientific, is a member of the Executive Board of the IASP Special Interest Group in Neuromodulation, and is newsletter liaison of the ASRA Neuromodulation SIG. M.J. Johnson, C. van den Abeele, and Y. Tan are employees of Medtronic. S. Bhatia, C. Burnette, M. Deruytter, B. Edmiston, V. Galan, G.G. March, T. Houden, S. Jaramillo, S.P. Lad, A. Lopez, C. Raftopoulos, T.-N. Vu, J. Vangeneugden, E. Tallarico, and C. Yepes declare no competing interests.

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Author contributions: The TSC consisting of principal investigator P. Rigoard (Chairman), and external advisors L. Annemans, M.J.D., R.S.T., K.K., and R. North designed the study, approved the analysis plan, provided study oversight, and contributed to the interpretation of the data. The PROMISE study group conducted the study and reviewed and approved the final article with considerable data contributions from S. Basu. P. Rigoard drafted the initial article with input and critical review from the T.S.C., C.V.D.A., M.J. Johnson, and Y. Tan. Y. Tan provided tables, figures, and statistical analysis, with oversight from R.S.T.
All logistical aspects of the study were managed and funded by Medtronic. Data were collected by investigational sites and analysed by Medtronic under the direction of the committee and followed a predefined statistical analysis plan. Medtronic personnel made no patient assessments, care decisions, or had any impact whatsoever on the physician or his team's care decisions.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A751.

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