North American Spine Society Journal (NASSJ) 19 (2024) 100528

Contents lists available at ScienceDirect

North American Spine Society Journal (NASSJ)

journal homepage: www.elsevier.com/locate/xnsj

Clinical Studies

Twelve-month results from a randomized controlled trial comparing differential target multiplexed spinal cord stimulation and conventional spinal cord stimulation in subjects with chronic refractory axial low back pain not eligible for spine surgery

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FDA device/drug status: Approved.

Author Disclosures: ***TW:*** Physician-Owned Distributorship: Procura Pain and Spine (C); Stock Ownership: North Pines Surgery Center (F); Consulting: Medtronic (D); Research Support (Investigator Salary, Staff/Materials)^: Medtronic (D). ***RJ:*** Consulting: Medtronic (B). ***WA:*** Nothing to disclose. ***VM:*** Nothing to disclose. ***BS:*** Nothing to disclose. ***EA:*** Nothing to disclose. ***LK:*** Stock Ownership: Nalu (Stock), Gamma Core (Stock); Speaking and/or Teaching Arrangements: Nevro (C), Avanos (B), Saluda (D); Scientific Advisory Board/Other Office: Avanos (C), Neuralace (C), Neuros (D), Presidio (B), Biotronik (B); Research Support (Investigator Salary, Staff/Materials): Nevro, Medtronic, Biotronik, Gimer, SAOL Therapeutics, Sollis, Man and Science, FUS, Saluda, Nalu, Neuralace, Neuros, Xalud (Amounts not disclosed). ***HC:*** Speaking and/or Teaching Arrangements: Medtronic (B); Research Support (Investigator Salary, Staff/Materials): Stimgenics (Amount not disclosed). ***AEN:*** Nothing to disclose. ***MF:*** Stock Ownership: Brixton Biosciences (300k shares), Celeri Health (2M shares), Aurora Spine (E); Consulting: Saluda Medical (B), Medtronic (D); Speaking and/or Teaching Arrangements: Medtronic (E), Mainstay Medical (C). ***YE***: Consulting: Saluda (B), SPR Therapeutics (A); Research Support (Investigator Salary, Staff/Materials): Medtronic, Avanos, SPR Therapeutics (Amounts not disclosed); Grants: NIH (Amount not disclosed). ***PK:*** Consulting: medtronic (B), biotronic (B); Speaking and/or Teaching Arrangements: Medtronic (B); Research Support (Investigator Salary, Staff/Materials): Medtronic, Biotronik, Abbott, Saluda, Boson Scientific (Amounts not disclosed). ***AAE:*** Consulting: Medtronic (C); Grants: Medtronic (Variable every year). ***KC:*** Stock Ownership: Higgs Boson Health, Nalu medical, Rune Labs, Mainstay, NXTSTIM, Accufix Medical, Douleur Therapeutics, Costal Research Institute (Amounts not disclosed); Consulting: Medtronic (F), Mainstay (D), Vertos (B). ***YM:*** Nothing to disclose. ***MS:*** Nothing to disclose. ***NH:*** Nothing to disclose. ***BG:*** Speaking and/or Teaching Arrangements: Medtronic (B); Trips/Travels: Medtronic (B); Grants: Medtronic, Abbott (Amounts not disclosed). ***MG:*** Nothing to disclose. ***PG:*** Consulting: Medtronic (B); Speaking and/or Teaching Arrangements: Medtronic (B); Trips/Travels: Medtronic (A); Scientific Advisory Board/Other Office Medtronic (B); Research Support (Investigator Salary, Staff/Materials): Medtronic (Amount not disclosed). ***MW:*** Speaking and/or Teaching Arrangements: Medtronic (B). ***RB:*** Nothing to disclose. ***AW:*** Nothing to disclose. ***PS:*** Nothing to disclose. ***SL:*** Stock Ownership: Nalu (Stock), NeuroOne (Stock); Consulting: Avanos, Abbott, Biotronik, Nalu, NeuroOne, Nevro, PainTeq, Saluda, SPR Therapeutics, Vertos (Amounts not disclosed); Research Support (Investigator Salary, Staff/Materials): Avanos, Averitas Pharma, Biotronik, Ethos Laboratories, Nalu, NeuraLace, PainTeq, Saluda, SPR Therapeutics (Amounts not disclosed). ***SD:*** Consulting: Medtronic (B). ***JB:*** Nothing to disclose. ***GG:*** Nothing to disclose. ***KW:*** Nothing to disclose. ***SF:*** Stock Ownership: Backstop Neural, SurgenTec, SynerFuse, Aurora Spine, Thermaquil, SPR Therapeutics, Saluda, CornerLoc, SpineThera, Neural Integrative Solutions (# of shares unknown for all); Consulting: Abbott (E), Medtronic (D), Saluda (D), Vertos (D), CornerLoc (D), Mainstay (D); Research Support (Investigator Salary, Staff/Materials): Aurora, Mainstay, Medtronic, Abbott, Vertiflex, Saluda, Nalu, CornerLoc, Biotronik (Amounts not disclosed). ***WP:*** Nothing to disclose. ***DC:*** Stock Ownership: SGX Medical (Unknown number of options, >25% ownership); Consulting: SGX Medical (F); Research Support (Investigator Salary, Staff/Materials): Medtronic (F). ***RV:*** Stock Ownership: SGX Medical (Unknown number of options, >25% ownership); Consulting: Medtronic (E), SGX Medical (F). Research Support (Investigator Salary, Staff/Materials): Medtronic (F).

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https://doi.org/10.1016/j.xnsj.2024.100528
Received 10 May 2024; Received in revised form 3 July 2024; Accepted 9 July 2024
Available online 17 July 2024
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ARTICLE INFO

Keywords:
Persistent spinal pain syndrome type 1
Nonsurgical candidates
Spinal cord stimulation
Randomized controlled trial
Differential target multiplexed SCS
Conventional SCS

ABSTRACT

Background: Successful treatments for intractable chronic low back pain (CLBP) in patients who are not eligible for surgical interventions are scarce. The superior efficacy of differential target multiplexed spinal cord stimulation (DTM SCS) to conventional SCS (Conv-SCS) on the treatment of CLBP in patients with persistent spinal pain syndrome (PSPS) who have failed surgical interventions (PSPS-T2) motivated the evaluation of DTM SCS versus Conv-SCS on PSPS patients who are non-surgical candidates (PSPS-T1).

Methods: This is a prospective, open label, crossover, post-market randomized controlled trial in 20 centers across the United States. Eligible patients were randomized to either DTM SCS or Conv-SCS in a 1:1 ratio. Primary endpoint was CLBP responder rate (percentage of subjects with ≥50% CLBP relief) at 3-month in randomized subjects who completed trialing (modified intention-to-treat population). Patients were followed up to 12 months. Secondary endpoints included change of CLBP and leg pain, responder rates, changes in disability, quality of life, patient satisfaction and global impression of change, and safety profile. An optional crossover was available at 6-month to all patients.

Results: About 121 PSPS-T1 subjects with CLBP and leg pain mostly associated with degenerative disc disease and radiculopathy and who were not eligible for spine surgery were randomized. CLBP responder rate with DTM SCS (93.5%) was superior to Conv-SCS (36.4%) at the primary endpoint. Superior CLBP responder rates (88.1%–90.5%) were obtained with DTM SCS at all other timepoints. Mean CLBP reduction with DTM SCS (6.52 cm) was superior to that with Conv-SCS (3.01 cm) at the primary endpoint. Similar CLBP reductions (6.23–6.43 cm) were obtained with DTM SCS at other timepoints. DTM SCS provided significantly better leg pain reduction and responder rate, improvement of disability and quality of life, and better patient satisfaction and global impression of change. 90.9% of Conv-SCS subjects who crossed over were CLBP responders at completion of the study. Similar safety profiles were observed between the two groups.

Conclusion: DTM SCS for chronic CLBP in nonsurgical candidates is superior to Conv-SCS. Improvements were sustained and provided significant benefits on the management of these patients.

Introduction

Spinal cord stimulation (SCS) is a well-established treatment modality in patients with chronic low back and leg pain [1–3]. The majority of high-level evidence focused on treating patients who have not achieved adequate pain relief from corrective spinal surgeries (Persistent Spinal Pain Syndrome, PSPS-type 2, PSPS-T2 [4]). Historically, the conventional SCS (Conv-SCS) programming approach have used paresthesia-based parameters. Recently, novel paradigms that include 10 kHz SCS [5], burst SCS [6], closed loop feedback [7], and differential target multiplexed SCS (DTM SCS) [8] have been introduced. Randomized controlled trials (RCTs) have shown them to be superior to the modest long-term relief provided by Conv-SCS for chronic low back pain (CLBP). Among these approaches, 10 kHz SCS [5] and DTM SCS [8], reported CLBP responder rate (percent of patients reporting ≥50% relief vs. baseline) of 80% or more, significantly superior to that with Conv-SCS (about 50%) at the 3-month primary endpoint, which was sustained at the 12-month follow up.

There are many patients who experience CLBP and have not undergone spinal surgeries (classified as PSPS-type 1, PSPS-T1[4]). Conventional medical management (CMM), including medication and physical therapy, has been the main alternative for these patients and is often inadequate. Unfortunately, opioid medication therapy may lead to undesirable side effects including addiction. Imaging is often performed to assess candidacy for back surgery, which may be indicated for patients with mechanical spine instability, severe spinal canal stenosis or nerve impingement. Unfortunately, for many PSPS-T1 patients where imaging does not reveal a clear cause of CLBP, or when comorbid medical conditions preclude an invasive surgical procedure, there are limited treatment options.

The improved CLBP relief obtained with 10 kHz and DTM SCS treatments in PSPS-T2 patients prompted their clinical evaluation for the treatment of low back and leg pain in PSPS-T1 patients who have been found ineligible for spine surgeries. An RCT evaluating 10 kHz SCS versus CMM demonstrated that 10 kHz was superior to CMM on relieving CLBP with 81% and 78% responder rates in those patients who were assessed at the 3-month endpoint and 12-month follow up, respectively [9]. A recent RCT comparing burst SCS and CMM demonstrated a CLBP responder rate of 73% for burst SCS at the 6-month endpoint [10].

This manuscript reports results of an RCT that evaluated DTM SCS versus Conv-SCS for the treatment of intractable CLBP and leg pain in a subset of PSPS-T1 patients who are not candidates for spine surgery. This is the first and only RCT in which Conv-SCS is used as an active control arm for this patient population. Additionally, this RCT provided

Table 1
Key eligibility criteria of the study.

Inclusion	Exclusion
Adult patients (≥ 18 y)	Previous lumbar spinal surgery (e.g., lumbar fusion, discectomy, laminectomy, laminotomy)
Candidate for SCS system as per labeled indication* (back pain with or without leg pain)	A medical, anatomical, and/or psychosocial condition that contraindicated the commercially available study neurostimulation system
Refractory axial CLBP with a neuropathic component and not eligible for spine surgery (e.g. lumbar fusion, discectomy, laminectomy, laminotomy)	Mechanical spine instability
Average CLBP intensity ≥ 6 cm on the 10 cm Visual Analog Scale (VAS)	An existing active implanted device
Stable pain medication regime for at least 30 d prior to enrollment	Diagnosis of a condition with inflammatory causes of back pain (e.g. onset of severe pain with activity), serious spinal pathology and or neurological disorders
Willing to not increase pain medications through the 3-mo visit	Experienced an interventional procedure, within 30 d prior to enrollment, to treat back and/or leg pain that provided significant pain relief
Willing and capable of giving written informed consent	Pain in other area(s) and/or medical condition requiring the regular use of significant pain medications
Willing and capable of subjective evaluation, read and understand written questionnaires	Pregnancy
Willing and able to comply with study-related requirements, procedures, and visits	Concurrent participation in another clinical study
	Unresolved major issues of secondary gain (e.g., social, financial, legal)
	Involved in an injury claim under current litigation or a pending or approved worker's compensation claim

* Indications included degenerative disc disease or herniated discs refractory to conservative and surgical interventions or patients with radicular pain syndrome.

an optional cross over, which provided an opportunity to evaluate the potential benefits of DTM SCS on salvaging non-surgical PSPS-T1 patients who might have been treated with Conv-SCS without adequate pain relief, and vice versa.

Materials and methods

Study design and patient selection

This multi-center, prospective, open-label, crossover, postmarket RCT has been designed to assess DTM SCS as compared with Conv-SCS in PSPS-T1 subjects with CLBP who were deemed ineligible to undergo spinal surgery. The study was conducted at 20 investigational sites across the United States. The study protocol and informed consent forms were approved by the WCG Institutional Review Board (WCG IRB, Princeton, NJ) and the Ochsner Clinic Foundation IRB (New Orleans, LA). This study was registered in clinicaltrials.gov (NCT04571242). Table 1 lists key eligibility criteria.

Randomization and masking

Qualified subjects were randomized 1:1 to DTM SCS or Conv-SCS. Randomization assignments were computer-generated and designated via a centralized secured Electronic Data Capturing (EDC) system by site using a random permuted block design, stratified by gender and whether the subject had leg pain or not at baseline. Due to the different nature of the treatment arms (programming algorithm to reduce paresthesia in DTM SCS vs programming to have paresthesia in Conv-SCS) and the optional crossover at the primary endpoint, masking of subjects and investigators was not possible.

Procedures

Randomized subjects underwent a standard SCS trial phase. Using fluoroscopic x-ray guidance, investigators placed one or two cylindrical percutaneous temporary leads (Vectris 1 × 8 compact, Medtronic, Minneapolis, MN) in the thoracic epidural space spanning the T8-T11 vertebral levels as described in the lead implant manual [11]. Leads were externally anchored and connected to a wireless external neurostimulator (WENS, 97725, Medtronic, Minneapolis, MN). Anterior-posterior (AP) and lateral x-ray images of the final position of the leads were obtained after lumbar flexion. SCS was programmed according to the randomization assignment by a site clinician assisted by a representative of either the device manufacturer for Conv-SCS or the study sponsor for DTM SCS. For Conv-SCS, therapy was programmed according to traditional practice [12,13]. For DTM SCS, therapy was programmed as previously described [8]. Briefly, subjects were given three therapy options to choose from, each consisting of multiple pulsed signals set with independent parameters (programs). Each DTM SCS option consisted of four signals multiplexed using four programs. In general, one program in each option consisted of a 50 Hz signal (200 μs pulse width, PW) and the other three consisted of signals at 300 Hz (170 μs PW). Each option delivered the multiplexed signals at different locations that accounted for variable anatomical characteristics of the subjects. Intensities were set according to a DTM SCS algorithm, starting at a percentage below the threshold for perception and working them up at regular intervals until reaching therapeutic levels. Subjects adjusted intensities and selected their DTM SCS options based on optimal pain relief. Subjects who had a "successful trial phase" (≥40% CLBP reduction from baseline) could advance to permanent implantation of a neurostimulation system. Two percutaneous permanent leads (Vectris Surescan 1 × 8 compact, Medtronic, Minneapolis, MN) were positioned and anchored at the location that rendered the successful Trial Phase before connecting to a neurostimulation system (Intellis 97715, Medtronic, Minneapolis, MN) placed in a subcutaneous pocket. AP and lateral x-ray imaging were obtained to document the position of the leads. Subjects who did not achieve a successful Trial Phase were discontinued from the study after removal of the leads.

An optional crossover to the other study arm was available to all subjects remaining in the study at the 6-month timepoint who were not successfully responding (i.e., experiencing <50% back pain relief relative to baseline) and were dissatisfied with the initially assigned treatment.

Measurements and outcomes

Standard patient-reported assessment tools were used. Back and leg pain levels were measured using a 10-cm VAS [14]. Functional disability was assessed using the Oswestry Disability Index (ODI) questionnaire [15], Quality of life was evaluated using the EQ-5D-5L questionnaire [16]. Likert scale-based questionnaires evaluated the Patient Global Impression of Change (PGIC) [17] and patient satisfaction. Measurements from these tools, along with reports of adverse events (AEs) were collected at baseline, end of the Trial Phase (EOT), and 1-, 3-, 6-, 9- and 12-month visits and securely recorded by the site researchers directly into the EDC system. Changes relative to baseline were assessed at the various time points. An individual responder to treatment was any subject who reported a decrease in pain ≥50% relative to baseline.

The primary endpoint was the CLBP responder rate defined as the percentage of individual responders to the assigned treatment (DTM SCS or Conv-SCS) at the 3-month. The primary outcome was the comparison of CLBP responder rates at the 3-month endpoint for a modified intention-to-treat (mITT) population using a non-inferiority hypothesis followed by a superiority hypothesis (see Statistical Analysis

for details). Secondary CLBP-related outcomes included the comparison of mean changes from baseline in CLBP VAS scores with study treatments at the 3-, 6-, 9- and 12-month visits, and the comparison of CLBP responder rates of study treatments evaluated at 6-, 9- and 12-month visits. Additional outcomes included the comparison of responder rates and mean changes from baseline in leg pain VAS scores for subjects who reported ≥5 cm baseline leg pain, the comparison of mean changes in ODI, and the comparison of mean changes in EQ-5D-5L indexes. Also, patient satisfaction and PGIC were collected. Analyses for postcrossover visits for test and control arms each included data of the subjects that crossed over, taking into account that subjects that crossed over were considered nonresponders to their original randomization assignment. Safety outcome was based on the frequency of treatment emergent AEs related to the study.

Statistical analysis

A sample size calculation based on a non-inferiority hypothesis for the primary endpoint between treatment groups using a one-sided (0.05 alpha level, ≥90% power) Farrington-Manning binomial test for proportions indicated that at least 50 subjects per group were required assuming a responder rate of 50% for the control arm and 20% difference with the test arm.

An intention to treat (ITT) population consisting of all randomized subjects was used in the analysis of the safety outcome. Given that a number of randomized subjects could be discontinued early from the study due to unforeseeable reasons (inability to place leads in the epidural space, non-compliance with study directions, lack of commercial insurance approval), the study design prespecified that a mITT population, consisting of subjects who completed the Trial Phase, was used for primary and secondary analyses. Subjects who failed the Trial Phase and subjects that withdrew from the study due to lack of effective CLBP relief before the 3-month endpoint were considered nonresponders toward the primary endpoint. Missing data toward primary and secondary analyses were accounted for using a repeated measures model imputation method. Analyses for additional outcomes used subjects within the mITT population who completed assessments while carrying forward data for nonresponders in the Trial Phase. Subjects that opted to cross over at the 6-month timepoint were considered nonresponders to their originally assigned treatment at this timepoint and their baseline data were carried forward. Subjects that crossed over contributed data to their new treatment in the 9- and 12-month analyses. Analyses for outcomes in the subjects that crossed over were done using the mITT population that completed assessments.

One-sided (0.05 alpha) Farrington-Manning binomial tests assessed the non-inferiority (10% margin) and superiority of DTM SCS compared to Conv-SCS for the primary endpoint. A p-value ≤.05 in each of the hypothesis tests indicated non-inferiority or superiority. Binomial tests were used for secondary endpoint analyses pertaining to binary outcomes. The statistical significance of comparisons of results from additional outcomes was calculated from 2 sample t-tests for continuous data and Fisher's Exact test for categorical data. Results are reported as mean ± standard deviation (SD) unless otherwise indicated.

All study-related AEs and serious adverse events (SAEs) were reported for the ITT population by treatment group. Rates were reported as the number of subjects who experienced at least one event during the analysis interval out of the total number of subjects who were treated.

Results

Study subjects

Study started on August-2020 and was completed on April-2023. Fig. 1 shows the disposition of subjects in the study. The Trial Phase was completed by 51 subjects in the DTM SCS (49 responders) and 54 in the Conv-SCS (42 responders). These comprised the mITT analysis population (3- and 6-month visits). For 9-, and 12-months, the analysis population for DTM SCS increased to 65 due to the additional subjects that crossed over.

Demographic and baseline data are displayed in Table 2. About 57% were female in the DTM SCS arm and 61% in the Conv-SCS arm. Age, BMI, and number of years with chronic pain were similar in both groups. Mean baseline CLBP VAS scores were also similar (7.9 and 8.0 cm for DTM and Conv-SCS). Mean baseline leg pain VAS scores including all subjects reporting leg pain was 6.7 cm for DTM SCS and 7.8 cm for Conv-SCS. This was the only baseline characteristic in which there was a statistically significant difference between the groups. All subjects had been diagnosed with a neuropathic pain component and 85.7% had leg pain at baseline. In terms of pain etiology, there were no significant differences in the distribution between the two arms. Radiculopathy was the etiology present in the largest percentage of subjects (88% in the DTM SCS and 85% in Conv-SCS) followed by degenerative disc disease (75% in DTM SCS, 78% in Conv-SCS).

Pain relief outcomes

Low back pain relief

CLBP responder rates at the 3-month primary endpoint were 93.5% (95% CI: 81.6%–97.9%) with DTM SCS, which was superior (p<.0001) to 36.4% (95% CI: 23.6–51.4) with Conv-SCS for the mITT populations using imputation of missing data. Responder rates without imputation were similar. A sensitivity analyses for the primary endpoint using a tipping point was carried out by considering worst- and best-case scenarios of the imputed data (5 subjects for DTM SCS and 10 subjects for Conv-SCS). In the worst-case scenario for DTM SCS, responder rate would be 84.3%, with 48.1% in the best-case scenario for Conv-SCS, which is still a superior (p<.0001) result for DTM SCS. Superiority of CLBP responder rate was sustained throughout the length of the study (Fig. 2). The responder rate for subjects who were implanted and completed the back pain assessment at the 3-month endpoint (PP analysis) was 97.7% for subjects treated with DTM SCS, which was superior (p=.0007) to the 53.3% obtained with Conv-SCS treatment.

Figs. 3 and 4 show CLBP VAS scores CLBP reduction relative to baseline for the mITT population using imputation. Treatments significantly reduced VAS scores, although DTM SCS was more efficacious. CLBP reduction of 6.52 cm (95% CI: 5.80–7.24) at the 3-month primary endpoint with DTM SCS was statistically superior (p<.0001) to the 3.01 cm (95% CI: 2.27–3.75) reduction with Conv-SCS. CLBP reduction due to DTM SCS was sustained and superior to Conv-SCS at all time points.

Leg pain relief

Fig. 5 shows leg pain VAS scores in patients with baseline leg pain VAS score ≥5 cm, and Fig. 6 shows leg pain responder rate (percentage of subjects with ≥50% leg pain relief) and reduction in leg pain relative to baseline for the mITT population using imputation. Leg pain responder rate with DTM SCS was 88.2% (95% CI: 72.5%–95.5%) at the 3-month visit, 93.3% (95% CI: 76.9–98.3%) at the 6-month visit and remained above 80% in subsequent visits. In contrast, leg pain responder rate with Conv-SCS decreased from 51.4% at 3 months to 22.9% at 12 months. Leg pain responder rate with DTM SCS was superior to Conv-SCS at all timepoints. Leg pain reduction with DTM SCS was superior to Conv-SCS, being 6.27 cm (95% CI: 5.39–7.16 cm) at 3-month, 6.44 cm (95% CI: 5.53–7.36 cm) at 6-month, and ≥6.0 cm at subsequent visits.

Other patient-reported outcomes

Extent of functional disability

Fig. 7 shows the reduction of the ODI relative to baseline. Data from subjects who crossed over was included and baseline data for nonresponders to trial was carried forward. A reduction of ODI reflects an improvement in the ability to function in daily life activities. Differences

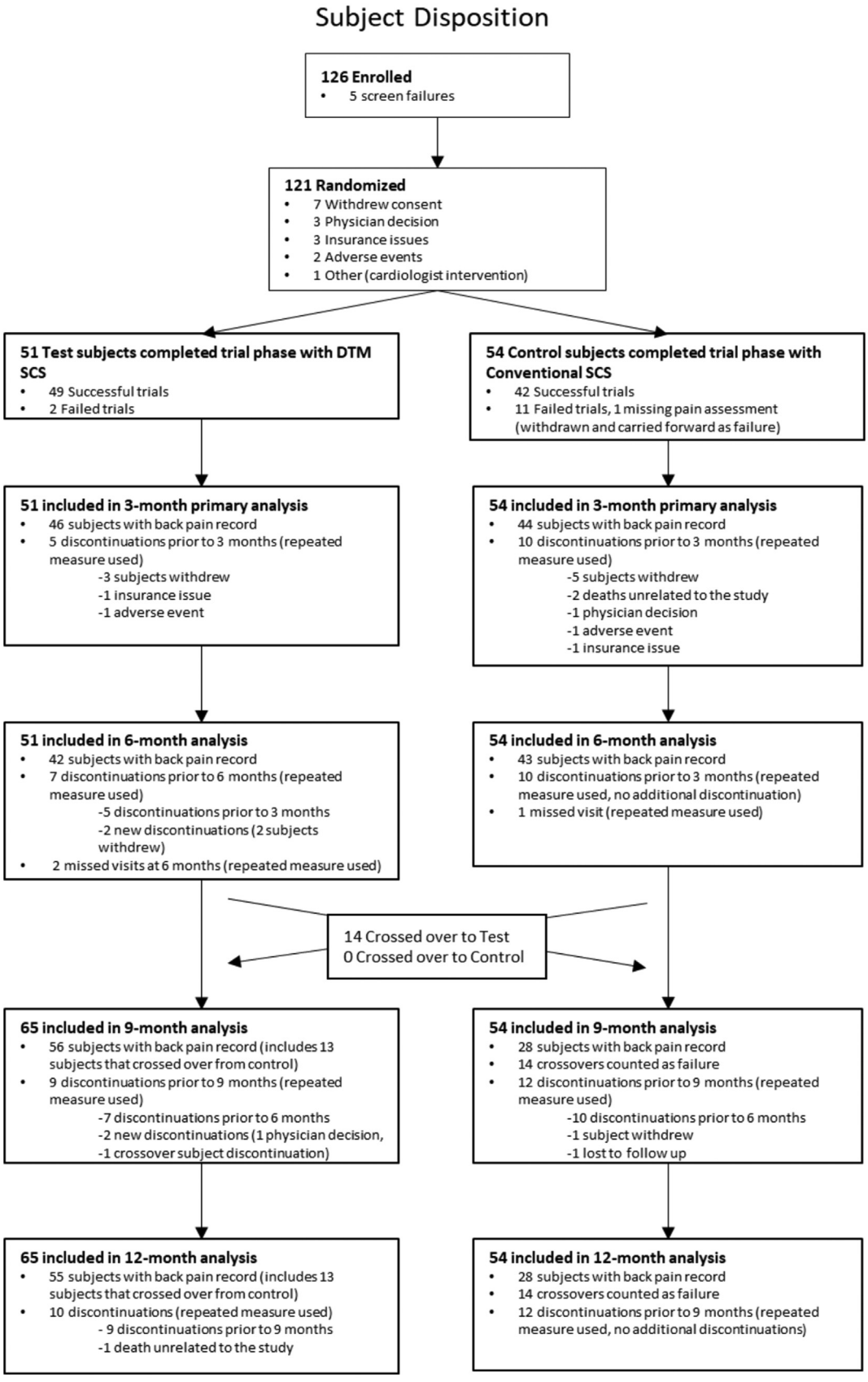

Fig. 1. Subject disposition of study subjects.

Table 2
Baseline demographics and characteristics of the study subjects (mITT population).

Characteristics	DTM SCS (N = 51)	Conv-SCS (N = 54)	p-value*
Sex N (%)			.695
Female / male	29 (56.9%) / 22 (43.1%)	33 (61.1%) / 21 (38.9%)	
Age (y)			.183
Mean ± SD	62.9 ± 13.5	59.6 ± 12.1	
BMI (kg/m^2)			.525
Mean ± SD	30.2 ± 4.5	30.9 ± 6.1	
Years with pain N (%)			.902
Mean ± SD	9.5 ± 8.0	9.4 ± 8.4	
Baseline back pain (VAS) (cm)			.857
Mean ± SD	7.9 ± 1.0	8.0 ± 1.1	
Leg pain n (%)(%)†	N = 45	N = 45	1.000
Unilateral	14 (31.1%)	15 (33.3%)	
Bilateral	31 (68.9%)	30 (66.7%)	
Baseline leg pain (VAS) (cm)†	N = 45	N = 45	.009
Mean ± SD	6.7 ± 2.4	7.8 ± 1.6	
Pain diagnosis			
Chronic intractable back pain	51 (100.0%)	54 (100.0%)	N/A
Chronic intractable leg pain	45 (88.2%)	45 (83.3%)	.581
Pain etiology			
Neuropathic pain	51 (100.0%)	54 (100.0%)	N/A
Radiculopathy	45 (88.2%)	46 (85.2%)	.777
Degenerative disc disease	38 (74.5%)	42 (77.8%)	.819
Spondylosis	35 (68.6%)	40 (74.1%)	.666
Mild/moderate spinal stenosis	27 (52.9%)	19 (35.2%)	.079
Lumbar facet-mediated pain	15 (29.4%)	13 (24.1%)	.660
Sacroiliac dysfunction	9 (17.6%)	6 (11.1%)	.409
Internal disc disruption/annular tear	8 (15.7%)	7 (13.0%)	.784
Spondylolisthesis	5 (9.8%)	5 (9.3%)	1.000
Other chronic pain	22 (43.1%)	29 (53.7%)	.331

* p-values for continuous data were calculated from two sample t-test. p-values for categorical data were calculated from Fisher's Exact test.

† Subjects with leg pain at baseline. Subgroup analysis was performed on baseline leg pain and there was no statistical evidence of a differential treatment effect for the significant difference at baseline.

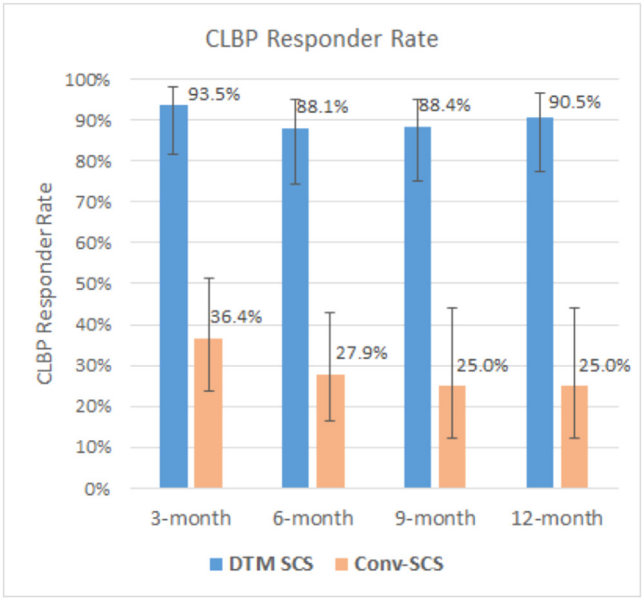

Fig. 2. Back pain responder rate at various time points of the study. Error bars are 95% CI. DTM SCS was superior at all time points. Results are obtained for the mITT using a repeated measures model for imputation of missing data. Crossover data was censored in this analysis.

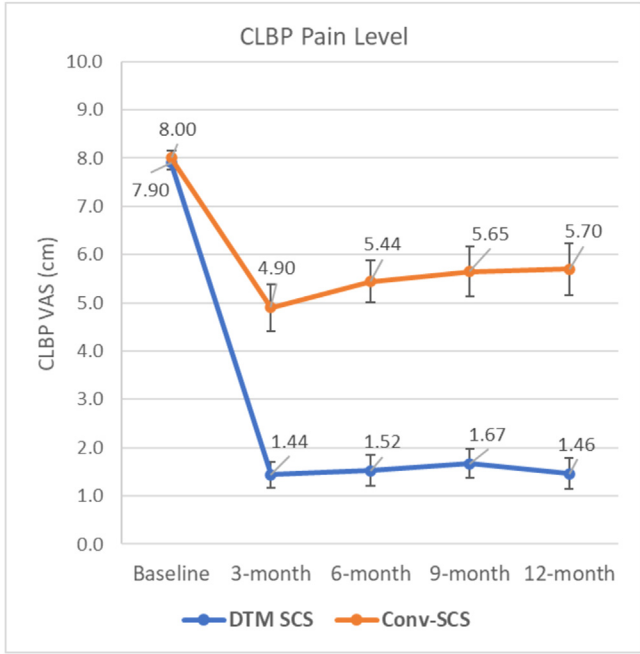

Fig. 3. Back pain VAS scores along the 12-month follow up visits for DTM SCS and Conv-SCS in the mITT population and with crossover data censored. Error bars correspond to standard errors.

in ODI changes between DTM SCS and Conv-SCS are statistically significant ($p<.01$) throughout the study. Improvement in ODI at 3-month with DTM SCS was 22.7 ± 12.4, down from 50.3 at baseline, which was sustained at 6-month (24.3 ± 15.5) and 12-month (23.5 ± 16.1). In contrast, improvement in ODI with Conv-SCS was about half of that provided by DTM SCS, being 12.0 ± 13.6 at 3-months, down from 47.9 at baseline, and 9.7 ± 13.9 at 12-months.

Changes in quality of life

Fig. 8 shows changes in EQ-5D-5L index and EQ-5D-5L VAS score. An increase of these values reflects an improvement in health and quality of life. Differences in EQ-5D-5L index changes due to DTM SCS and Conv-

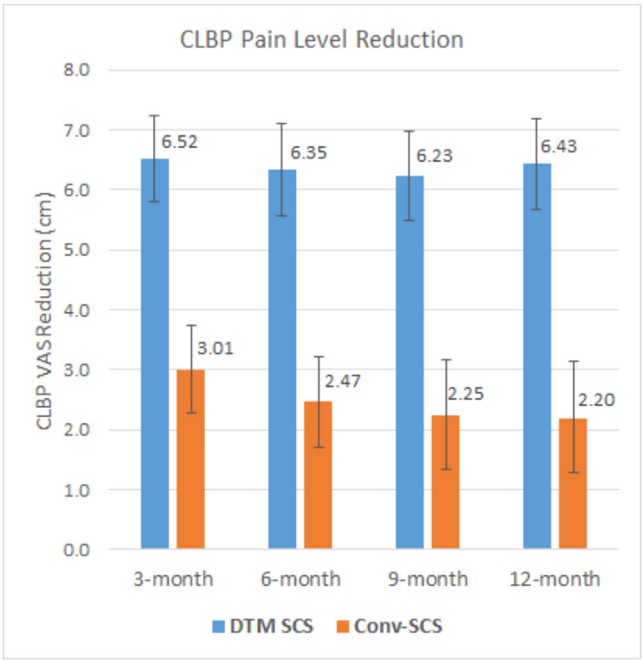

Fig. 4. Back pain reduction relative to baseline at the various time points of the study. Error bars are 95% CI. DTM SCS was superior at all time points. Results were obtained for the mITT population using a repeated measures model for imputation of missing data. Crossover data was censored in this analysis.

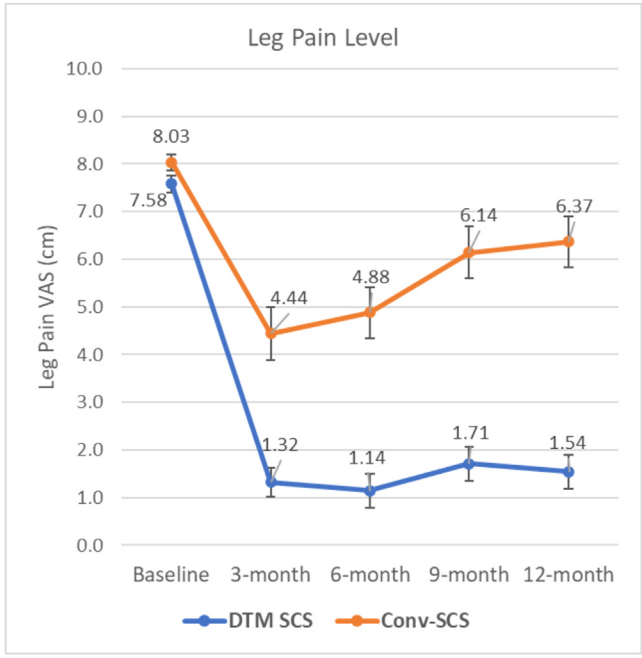

Fig. 5. Leg pain VAS scores along the 12-month follow up visits for DTM SCS and Conv-SCS in the mITT subjects with baseline leg VAS ≥ 5 cm, including the record for subjects that crossed over from the control to the test arm. Error bars correspond to standard errors.

SCS were statistically significant ($p<.01$) at all timepoints. EQ-5D-5L index at 3-month increased with DTM SCS (0.230 ± 0.172, up from 0.513 at baseline), which was sustained at 6-month (0.237 ± 0.151) and 12-month (0.232 ± 0.162). In contrast, the increase in EQ-5D-5L index with Conv-SCS was 0.115 ± 0.124 at 3-months, up from 0.547 at baseline, and slightly lower at 6- and 12-month (0.094 ± 0.150 and 0.090 ± 0.128, respectively).

Satisfaction, and impression of change

Tables 3 and 4 show satisfaction and PGIC. About 93% of subjects treated with DTM SCS were very satisfied/satisfied at 3-month. This level was sustained at subsequent timepoints. These were better than those reported with Conv-SCS before crossover. Similarly, PGIC with DTM SCS was better than with Conv-SCS. About 91% of subjects treated with DTM SCS reported to be very much improved/much improved at 3-month, in contrast to 73% with Conv-SCS. This level of improvement with DTM SCS was sustained at the later study timepoints.

Crossover outcomes

None of the subjects randomized to DTM SCS crossed over to Conv-SCS. Fourteen out of the 30 subjects (46.7%) in Conv-SCS who com-

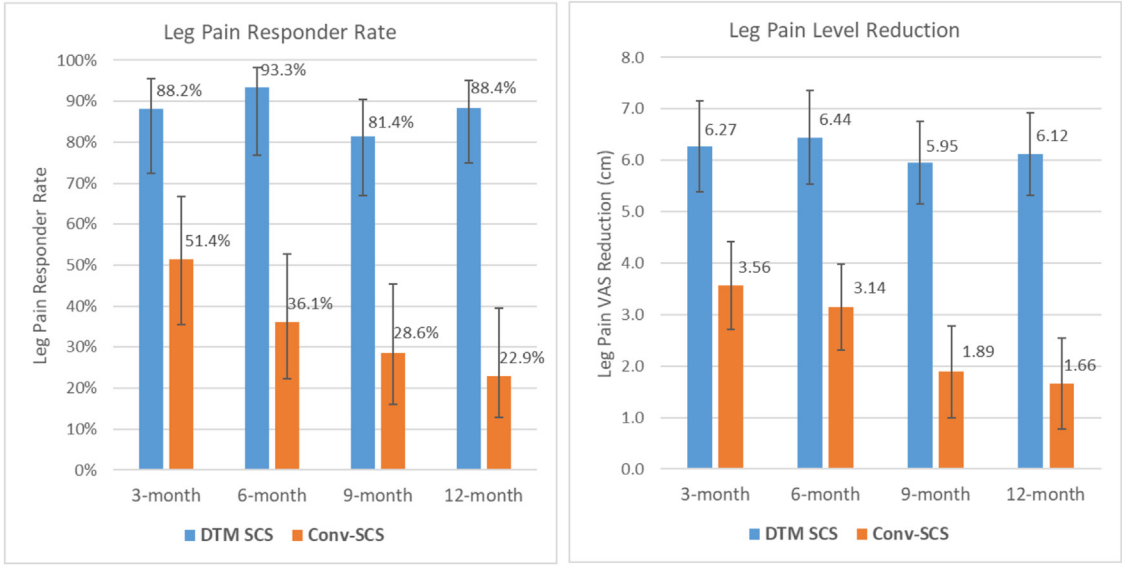

Fig. 6. Leg responder rate (left graph) and leg pain reduction from baseline (right graph) at various time points of the study. Error bars are 95% CI. DTM SCS was superior at all time points. Results obtained for the mITT using a repeated measures model for imputation of missing data, including the record from subjects that crossed over from Conv-SCS to DTM SCS at the 6-month visit.

Table 3
Patient satisfaction results.

		Very satisfied	Satisfied	Not sure	Dissatisfied	Very dissatisfied
3-mo	DTM SCS	33 (75.0%)	8 (18.2%)	0 (0.0%)	1 (2.3%)	2 (4.5%)
	Conv-SCS	13 (43.3%)	13 (43.3%)	4 (13.3%)	0 (0.0%)	0 (0.0%)
6-mo	DTM SCS	32 (80.0%)	4 (10.0%)	3 (7.5%)	1 (2.5%)	0 (0.0%)
	Conv-SCS	13 (44.8%)	8 (27.6%)	6 (20.7%)	2 (6.9%)	0 (0.0%)
9-mo	DTM SCS	38 (70.4%)	14 (25.9%)	1 (1.9%)	1 (1.9%)	0 (0.0%)
	Conv-SCS	8 (57.1%)	5 (35.7%)	0 (0.0%)	1 (7.1%)	0 (0.0%)
12-mo	DTM SCS	40 (75.5%)	9 (17.0%)	2 (3.8%)	1 (1.9%)	1 (1.9%)
	Conv-SCS	7 (50.0%)	5 (35.7%)	1 (7.1%)	0 (0.0%)	1 (7.1%)

Table 4
Patient global impression of change (PGIC) results.

	3-mo		6-mo		9-mo		12-mo	
	DTM SCS	Conv-SCS	DTM SCS	Conv-SCS	DTM SCS	Conv-SCS	DTM SCS	Conv-SCS
Very much improved	23 (52.3%)	8 (26.7%)	26 (65.0%)	9 (31.0%)	24 (44.4%)	4 (28.6%)	30 (56.6%)	7 (50.0%)
Much improved	17 (38.6%)	14 (46.7%)	9 (22.5%)	10 (34.5%)	24 (44.4%)	7 (50.0%)	17 (32.1%)	5 (35.7%)
Minimally improved	2 (4.5%)	6 (20.0%)	3 (7.5%)	6 (20.7%)	4 (7.4%)	2 (14.3%)	3 (5.7%)	2 (14.3%)
No change	1 (2.3%)	2 (6.7%)	1 (2.5%)	3 (10.3%)	0 (0.0%)	0 (0.0%)	2 (3.8%)	0 (0.0%)
Minimally worse	1 (2.3%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	2 (3.7%)	0 (0.0%)	1 (1.9%)	0 (0.0%)
Much worse	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)
Very much worse	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

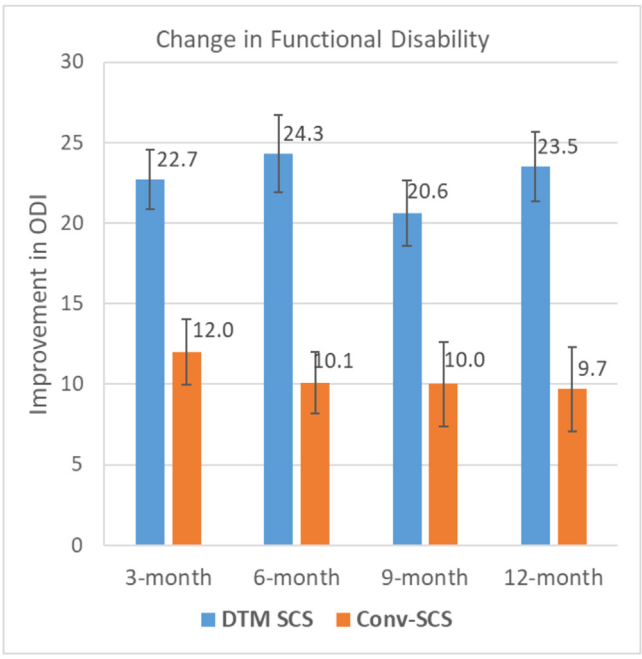

Fig. 7. Improvement in functional disability (ODI) along the 12-month visits for DTM SCS and Conv-SCS. Error bars correspond to standard errors. Differences of mean improvement between treatments are significant.

pleted the 3-month primary endpoint opted to cross over to DTM SCS. One of these subjects withdrew before the 9-month visit. Out of the remaining, 12 were CLBP responders to DTM SCS at the 9-month and 12-month visit. CLBP reduction went from 2.33 ± 2.75 cm with Conv-SCS at the 6-month crossover timepoint to 5.95 ± 2.24 cm with DTM SCS at the 12-month visit. 9 of 11 subjects who crossed over with baseline leg pain ≥5 cm ended the study being leg pain responders to DTM SCS. Mean leg pain reduction was 6.00 ± 2.43 cm with DTM SCS at the final visit, a large improvement when compared to the 3.35 ± 2.51 cm due to Conv-SCS at the time of crossover.

When considering together subjects randomized to treatment with DTM SCS and those who crossed over, the mITT population treated with DTM SCS at the 9- and 12-month study visit consisted of 65 subjects. CLBP responder rates of 89.3% (95% CI: 78.1–95.1%) and 90.9% (95% CI: 80.0%–96.2%) were obtained at the respective visits after missing data was imputed. CLBP VAS reduction from baseline were 6.13 cm (95% CI: 5.45–6.80 cm) at 9-month and 6.32 cm (95% CI: 5.64–7.00 cm) at 12-month. Corresponding leg pain responder rates were 81.4% (95% CI: 67.0%–90.4%) and 88.4% (95% CI: 74.9%–95.1%) and leg pain VAS reduction from baseline were 5.95 cm (95% CI: 5.15–6.75 cm) and 6.12 cm (95% CI: 5.32–6.92 cm).

Safety outcomes

Table 5 shows a summary of study-related AEs. There were 28 study-related AEs involving 16.5% of the randomized subjects. There were 4 SAEs in 3 subjects, which were procedure related. Two SAEs were recorded from one subject who developed a spinal epidural hematoma and paralysis. The other 2 were respiratory arrest while under anesthesia and post-dural puncture headache. No device-related AE was serious or unanticipated. No study-related deaths were reported. To date, 3 of the SAEs had been resolved and one (paralysis) was still ongoing.

Procedural related incidents were the most common study-related AE, accounting for 53.6% of AEs. Four were pocket pain (14.3%) and another 4 were lead malfunction (14.3%). There were 4 lead migrations (14.3%), 3 of each (10.7%) of post-procedure pain, and allergic reaction, as well as 2 overstimulation, 2 infections at site and 1 IPG malfunction. Three of these required lead surgical revision, and 3 required surgical revision of the IPG. Only 1 patient was explanted.

Discussion

This RCT demonstrated that DTM SCS provides superior CLBP relief when compared with Conv-SCS in a subset of PSPS-T1 patients with intractable CLBP and leg pain deemed not eligible for spinal surgery. This is the only RCT in which a novel approach such as DTM SCS is compared to an active control SCS in this patient population. The superior efficacy of DTM SCS was sustained throughout 12-month. CLBP responder rates with DTM SCS were ≥85% at every timepoint. Despite PSPS-T1 patients being a more difficult-to-treat population, responder rates were consistent to those reported when using DTM SCS for CLBP in PSPS-T2 patients

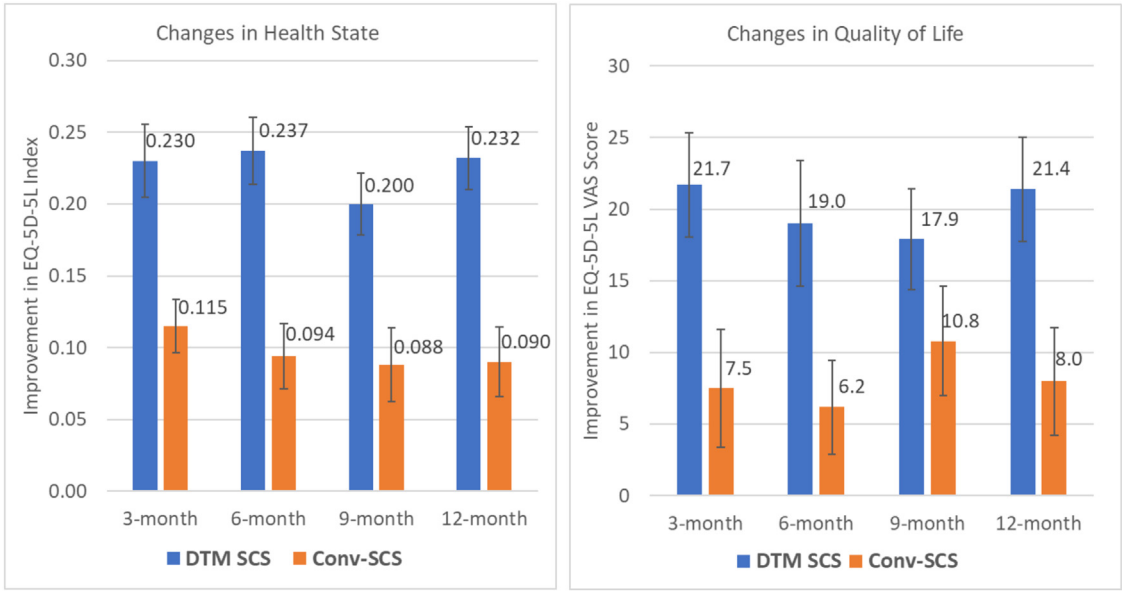

Fig. 8. Change in EQ-5D-5L index (left graph) and EQ-5D-5L VAS score (right graph) relative to baseline along the 12-month visits for DTM SCS and Conv-SCS. Error bars correspond to standard errors. Differences between mean improvement between treatment are significant for all comparisons except for EQ-5D-5L VAS score at 9 months.

Table 5
Summary of adverse events through the 12-month follow up of study subjects.

	DTM SCS (N = 63)		Conv-SCS (N = 58)		Total (N = 121)	
	# AEs	Subjects with AEs	# AEs	Subjects with AEs	# AEs	Subjects with AEs
All study-related AEs	19	13 (20.6%)	9	7 (12.1%)	28	20 (16.5%)
Study-related SAEs	2	1 (1.6%)	2	2 (3.4%)	4	3 (2.5%)
Procedure-related AEs	11	9 (14.3%)	4	4 (6.9%)	15	13 (10.7%)
Device-related AEs	3	2 (3.2%)	4	3 (5.2%)	7	5 (4.1%)

SAEs, serious adverse events; Study-related AE, any AE that is deemed to be related to the treatment by the investigator; Procedure-related AE, any study-related AE that is deemed to be related to the procedures associated with implanting the device; Device-related AE, any study-related AE that is deemed to be related to the functioning of the device.

[8]. CLBP responder rates with DTM SCS are among the highest when considering RCTs evaluating other SCS modalities on a similar population of PSPS-T1 patients not eligible for spine surgery [9]. Superior reduction of CLBP level from baseline with DTM SCS was more than 6.2 cm. This corresponds to ≥78% CLBP relief and is congruent with previously reported values using DTM SCS for CLBP in PSPS-T2 subjects [8]. These are also among the highest reductions reported in RCTs [9,10].

Improvement of leg pain with DTM SCS in patients reporting a VAS score ≥ 5 cm at baseline was also superior to Conv-SCS. Leg responder rate with DTM SCS was ≥81% at all the timepoints, with a mean reduction in leg pain VAS score ≥6 cm. This reduction is comparable to that reported in other RCTs [8–10], including that reported using DTM SCS for PSPS-T2 patients [8].

Subjects who opted to cross over from Conv-SCS to DTM SCS also experienced similar improvement. This demonstrates, for the first time, that it is possible to use DTM SCS to rescue non-surgical PSPS-T1 with CLBP and leg pain who have been ineffectively treated with Conv-SCS.

DTM SCS significantly reduced the extent of disability and improved the quality of life, translating into considerable PGIC and satisfaction. The 21–24 points reduction in mean ODI during the study period is about twice the minimally clinical important difference (MCID) previously reported [18]. Considering that the baseline ODI (around 50) represents a crippled population, a reduction of 24 points with DTM SCS translates into an improvement of two ODI categories, representing a mean population with moderate disability. Furthermore, the 0.20–0.24 improvement in EQ-5D-5L index due to DTM SCS treatment is also more than twice the MCID previously reported [19]. 90%–96% of patients treated with DTM SCS also felt very satisfied/satisfied. This extent of satisfaction was larger than the one reported with Conv-SCS. The difference is larger when considering that 70%–80% of patients treated with DTM SCS felt very satisfied, in contrast with 43%–57% reported by those treated with Conv-SCS.

Attrition rates within the mITT population in the DTM SCS arm, excluding subjects who failed the trial phase and thus exited the study, were 7.8% at permanent implant, 9.8% at the 3-month endpoint, and 17.6% at completion. These rates are not dissimilar to those found in other SCS RCT's [6–10]. For example, in another SCS RCT using non-surgical PSPS-T1 patients, attrition rates for the test arm were 6.3%, at permanent implant, 7.5% at 3-months, and 12.5% at 12-months [9]. Another RCT with a similar population reported 16.2% at 6-month [10]. The Conv-SCS arm in the current study experienced a higher attrition rate, being 20.4% at the time of permanent implant. Interestingly, 8 out of 42subjects who reported a successful Trial Phase with Conv-SCS withdrew consent before permanent implant. It is noteworthy to mention that this study was carried out in the middle of the Covid-19 pandemic, therefore the risk of exposure to viral infection in a hospital setting may have overcome the benefit of the marginal pain relief obtained during the Trial Phase. Post-implant attrition rates were low, being 2.2% for DTM SCS and 6.3% for Conv-SCS at the 3-month primary endpoint and 11.1% and 15.6% respectively at the study completion. These are within the expected range based on attrition in other RCTs [7,8]. It is interesting to note that post-implant attrition rate for Conv-SCS arm in the PSPS-T2 study evaluating DTM SCS vs. Conv-SCS was larger than the current study for PSPS-1 patients. This may be due to the crossover op-

tion in the current study that allowed control subjects to continue the study with DTM SCS treatment rather than withdrawing due to inadequate pain relief. Indeed, 13 out of the 14 subjects who crossed over completed the study.

This is the first RCT in which a novel programming approach is compared to Conv-SCS in a population of PSPS-T1 patients who suffer from intractable CLBP and are not surgical candidates. Baseline CLBP level was around 8 cm, meaning that patients were experiencing severe back pain. Most CLBP in patients was associated with radiculopathy (87%), degenerative disc disease (76%), spondylosis (71%), and/or mild/moderate spinal stenosis (44%). The superior performance of DTM SCS at providing CLBP relief as well as significantly better reduction of functional disability and improvement in quality of life implies that DTM SCS is a suitable alternative for PSPS-T1 patients who have no further therapeutical options. It is interesting to note that Conv-SCS did not seem to perform adequately at sustainably reducing CLBP in the PSPS-T1 population of this study despite the fact that 77.8% of patients reported a successful trial. Of those that were implanted and completed the primary endpoint visit, 53.3% reported ≥50% relief. By the 6-month follow up visit, the responder rate in this population had dropped to 41.4%. Notably, all patients but one that crossed over and completed the study were responders with DTM SCS, suggesting that DTM SCS may be used to rescue PSPS-T1 patients not eligible for spine surgery and who had been inadequately treated with Conv-SCS.

The incidence of study-related AEs and SAEs were consistent with what was anticipated based on other SCS studies [5–10]. There were no device-related SAEs.

Due to inherent differences of the DTM SCS and Conv-SCS programs, subjects, physicians, or clinical site personnel could not be blinded, which is a limitation of the study. Efforts were made to reduce bias during study design. Consistent with a previous implementation, programming support for DTM SCS was provided by representatives of the sponsor and that for Conv-SCS by representatives of the device manufacturer. This reduced preference bias toward the test arm that could be introduced when programming support of both arms is provided by representatives of a single organization since it was in the interests of representatives from the sponsor and device manufacturer to support their respective patients optimally.

The study provided the option to cross over in order to rescue patients who felt inadequately treated with their allocated treatment at the 6-month post-device activation. Although this provided a potential benefit to patients, the inability to cross over at other time points may have hindered the benefits to other patients who may have needed it at a later time. The study was also not designed to cross over to the other treatment arm for subjects who failed the trial phase, or those who were not satisfied with their treatment before the 6-month cross over timepoint.

As with many other studies, the primary outcome was mainly based on self-reported pain level. Although it would have been better to utilize a primary outcome that combined pain level and other patient-reported outcomes such as changes in functional disability and/or quality of life, the lack of previously standardized and validated methods to report combined outcomes at the time of study design prevented such approach. It is encouraging to see, however, that improvements in disability and quality of life, as well as levels of satisfaction and global impression of change are consistent with the CLBP responder rate based on pain relief assessments.

Conclusion

CLBP responder rate with DTM SCS for nonsurgical PSPS-T1 patients with degenerative disc disease and radiculopathy was statistically superior to that with Conv-SCS throughout the duration of the study. Significantly greater reduction in CLBP and leg pain levels relative to baseline were also observed with DTM SCS throughout the study. Consistent with superior pain relief, improvements in functional disability and quality of life with DTM SCS were significantly better than those obtained with conventional SCS and surpassed by large margin what is considered the minimally clinical improvement value, demonstrating that DTM SCS provided robust and positive benefits that were sustained over time. The frequency, type, seriousness, and severity of study-related AEs were similar in both groups and demonstrated an acceptable risk profile. The superior benefits of the DTM SCS programming offers clinicians and PSPS-T1 patients who are not surgical candidates a highly efficacious option for the treatment of intractable chronic back pain.

Declarations of competing interests

One or more of the authors declare financial or professional relationships on ICMJE-NASSJ disclosure forms.

Acknowledgments

Thanks to other coinvestigators, research coordinators, technical and nursing staff at the study sites for their valuable contributions.

Funding

This study was sponsored by SGX NOVA LLC, an independent clinical research company, which was acquired by Medtronic Inc after the study had been completed and closed. No employees of Medtronic Inc. were involved in either data analysis or drafting, or authorship of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xnsj.2024.100528.

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