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An implantable restorative-neurostimulator for refractory mechanical chronic low back pain: a randomized sham-controlled clinical trial

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Abstract

Chronic low back pain can be caused by impaired control and degeneration of the multifidus muscles and consequent functional instability of the lumbar spine. Available treatment options have limited effectiveness and prognosis is unfavorable. We conducted an international randomized, double-blind, sham-controlled trial at 26 multidisciplinary centers to determine safety and efficacy of an implantable, restorative neurostimulator designed to restore multifidus neuromuscular control and facilitate relief of symptoms (clinicaltrials.gov identifier: NCT02577354). Two hundred four eligible participants with refractory mechanical (musculoskeletal) chronic LBP and a positive prone instability test indicating impaired multifidus control were implanted and randomized to therapeutic (N = 102) or low-level sham (N = 102) stimulation of the medial branch of the dorsal ramus nerve (multifidus nerve supply) for 30 minutes twice daily. The primary endpoint was the comparison of responder proportions (≥30% relief on the LBP visual analogue scale without analgesics increase) at 120 days. After the primary endpoint assessment, participants in the sham-control group switched to therapeutic stimulation and the combined cohort was assessed through 1 year for long-term outcomes and adverse events. The primary endpoint was inconclusive in terms of treatment superiority (57.1% vs 46.6%; difference: 10.4%; 95% confidence interval, −3.3% to 24.1%, $P = 0.138$). Prespecified secondary outcomes and analyses were consistent with a modest but clinically meaningful treatment benefit at 120 days. Improvements from baseline, which continued to accrue in all outcome measures after conclusion of the double-blind phase, were clinically important at 1 year. The incidence of serious procedure- or device-related adverse events (3.9%) compared favorably with other neuromodulation therapies for chronic pain.

Keywords: Restorative neurostimulation, Multifidus muscle, Impaired neuromuscular control, Functional segmental stability, Chronic low back pain, Randomized controlled trial, Active sham, Mechanical chronic low back pain

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

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1. Introduction

Low back pain is the leading cause of years lived with disability worldwide and often a determinant for chronic opioid use.[43,49,64] In the United States, direct healthcare spending on low back and neck pain is estimated at $87.6 billion and growing at a rate of 6.5% annually,[22] and indirect costs including disability benefits and days of work missed are estimated to be as high as $624.8 billion.[15] Most cases of acute low back pain (LBP) resolve spontaneously without treatment, but chronic LBP (CLBP) is far less likely to resolve on its own.[52] Patients with CLBP often endure impaired quality of life, depression, anxiety, and sleep disturbance.[3,7]

The majority of patients with CLBP have no indication for spine surgery but are suffering from mechanical (musculoskeletal) pain that is predominantly nociceptive.[5,21,36] Although nonsurgical treatments, including physical therapy, chiropractic care, non-opioid and opioid medications, injections, and medial branch rhizotomy, provide modest relief and improved function for some, they are ineffective or provide only transient relief for many.[1,4,8,10,29,63,65,68,72,84] Although spinal cord stimulation is an option to be considered for individuals who have failed multiple other treatments and have disabling symptoms related to neuropathic leg and LBP, it is not considered appropriate for the treatment of mechanical CLBP.[19,80]

Mechanical CLBP is often associated with impaired motor control and degeneration of the multifidus muscles, which play an important role in providing segmental control of functional lumbar spine stability.[37,55,73,79] Acute back pain–induced disruption of proprioceptive signaling is believed to facilitate long-term motor control changes via cortical reorganization.[58] This hypothesis is supported by experimental and clinical findings. For example, experimentally induced disk or nerve root injury reduces multifidus neural drive,[48] and in patients with mechanical CLBP, electromyographic activity and ability to recruit the multifidus muscle is diminished.[16]

Although motor control exercises for mechanical CLBP seem to be more effective in the short-term than other exercises, their long-term effectiveness is limited.[10,74] One possible explanation for this is that isolated muscle activation, which is required to reverse impaired motor control,[47,81] is difficult to achieve voluntarily, especially in the presence of underlying inhibition of the multifidus muscle. Furthermore, the structural changes in the muscle and cortical remodeling observed in patients with mechanical CLBP are likely to require longer treatment duration.[47,82]

Based on these insights, it was proposed that eliciting isolated multifidus activation by electrically stimulating the medial branch of the dorsal ramus nerve could facilitate restoration of segmental control and functional stability, and enable symptom reduction.[66]

Encouraging clinical results from a feasibility study led to the development of an implantable, restorative-neurostimulator (ReActiv8; Mainstay Medical, Dublin, Ireland).[17] A prospective multicenter single-arm clinical study supported European regulatory approval for the system in 2016,[18] and informed the development of the ReActiv8-B pivotal trial, designed to determine the safety and efficacy of this restorative-neurostimulator under an investigational device exemption from the United States Food and Drug Administration (FDA). The primary objective of this trial was to test the hypothesis that at the end of the 120-day blinded phase, there would be a greater proportion of responders in the treatment group that received therapeutic stimulation than in the sham-control group that received low-level sham stimulation.

2. Methods

2.1. Trial design and oversight

ReActiv8-B was a prospective, parallel-group, randomized, double-blind, sham-controlled clinical trial of this novel neuromuscular restorative-stimulation system in 26 multidisciplinary centers in the United States, Australia, and Europe. Trial design incorporated recommendations from FDA guidance,[33,56] the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials,[25–27,51,54] and the National Institutes of Health Task Force on Research Standards for CLBP.[20]

Conduct of the trial complied with the FDA regulations, ISO 14155, International Conference on Harmonization, and the Declaration of Helsinki. Local institutional review board or ethics committee approval was obtained at each site, and the results are reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines.[59]

Independent trial oversight included a clinical events committee (CEC), a data monitoring committee (DMC), and a magnetic resonance imaging (MRI) review committee.

The role of the DMC was to periodically review trial results, evaluate the treatments for excess adverse effects, determine whether the basic trial assumptions remain valid, judge whether the overall integrity and conduct of the trial remain acceptable, and make recommendations to the sponsor with respect to continuation of the study. With exception of the interim analysis and the primary endpoint analysis, all aggregate data were reported to the DMC in a blinded fashion (ie, group A and group B).

The role of the CEC was to review medication changes and adjudicate all adverse events for classification appropriateness according to the Medical Dictionary for Regulatory Activities (MedDRA version 19.1) level of severity, relatedness to device and/or procedure, and resolution. Committee members remained blinded to participant randomization assignment and clinical site.

The role of the MRI review committee was to review each patient's MRI at enrollment to ensure the patient was not a candidate for spinal surgery using common assessment criteria. Reviewers also noted whether other criteria required reassessment.

Implanting physicians at each participating site were required to complete formal implant procedure and prone instability test training.

2.2. Participants

Patients with disabling mechanical CLBP were evaluated for eligibility at each of the participating specialist pain centers and provided consent before enrollment. Participants were 22 to 75 years of age and had a diagnosis of (nonneuropathic) mechanical CLBP with pain on at least half of the days in the prior year, and continuing LBP despite >90 days of medical management, which included medication prescribed and used for CLBP and at least one past or new attempt of physical therapy treatment for LBP for which no specific program or duration was specified; reported a 7-day recall of average LBP of ≥6.0 and ≤9.0 cm on the 10-cm visual analogue scale (VAS); had an Oswestry Disability Index (ODI) of ≥21 and ≤60 points on a scale from 0 to 100; and had a positive prone instability test suggesting

impaired motor control of the multifidus muscle and consequent lumbar segmental instability.[46] Furthermore, candidates were excluded if they had prior lumbar spine surgery below T8 or spinal fusion at any level; a pathology seen on MRI that was clearly identified as the likely cause of CLBP and that was amenable to surgery; leg pain worse than back pain, or radiculopathy below the knee; neurological deficit possibly associated with the back pain; the source of pain was the sacroiliac joint as determined by the investigator; any surgical correction procedure for scoliosis at any time, or a current clinical diagnosis of moderate to severe scoliosis (Cobb angle ≥25°); any comorbid pain conditions (for interference with pain assessment); any previous rhizotomy or rhizolysis procedure on the dorsal root ganglion or medial branch at or below T8 within the prior year; any anesthetic block or injection of epidural steroids at or below T8 in the 30 days before the baseline visit; current baseline opioid use of more than 120 mg of morphine equivalent per day; any pain-related disability compensation or litigation issues; and evidence of an active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, compliance with intervention, and/or ability to evaluate treatment outcome (eg, active depression) as determined by a psychologist or psychiatrist. Unabridged enrollment criteria are provided in Supplement 1.

2.3. Randomization and blinding

Randomization was performed after implant surgery to avoid any procedure-related bias, and participants were randomly assigned in a 1:1 ratio to administer optimized therapeutic stimulation (treatment group) or low-level sham stimulation (control group). Randomization used a permuted block scheme for each investigational site. To maintain blinding, the assignment was obtained directly from the database developed and maintained by an independent contract research organization (CRO) during the randomization/activation visit approximately 14 days post-implant. The system generated a code that only the sponsor field clinical engineer responsible for programming the device could associate with the randomization assignment. The field clinical engineer had no access to any of the participant outcomes. Study monitors from 3 supporting independent CROs only had access to the randomization assignments for participants at their assigned subset of sites. Participants, treating physicians and site staff who collected participant outcome data, members of the oversight committees, and the sponsor and their representatives remained blinded to randomization assignment for the full blinded phase of the trial. Thus, only the independent CRO statisticians responsible for preparing reports had full access to the randomization and outcomes for all subjects. The DMC only saw the unblinded aggregate efficacy results at the interim analysis and after completion of the full blinded phase of the trial.

To manage neutral and equal expectations in both groups, participant instructions were scripted. All participants followed the same visit schedule and were instructed and trained to deliver two 30-minute stimulation sessions per day while in prone or side-laying position using their wireless activator; all were told that during the session, they "may or may not perceive stimulation"; all questionnaires were completed before any interaction with the participant; devices were programmed according to the group assignment but simulated parameter changes were done on the sham-control group to avoid bias by the length of the visit or the type of interaction during programming; an independent observer from the site attended all blinded visits to ensure that dialogue was similar with participants in both groups. Costs for devices, procedures, and medical visits related to the trial were covered by the sponsor for all participants; therefore, no risk of unblinding by insurance billing existed.

After the primary endpoint assessment at 120 days, blinding effectiveness was assessed by asking participants "Do you think you are in the treatment or in the control group?" Subsequently, participants were unblinded to their assignment and those receiving sham stimulation were offered therapeutic stimulation. Measures to maintain blinding and equipoise are summarized in Table S1.

2.4. Procedures

All participants were permanently implanted with the system (**Fig. 1**). Follow-up visits were done at 14, 45, 75, and 120-days after randomization, and during the open-label phase at 6, 9, and 12 months and annually thereafter for a total of 5 years after randomization (Fig. S1). After the blinded phase and primary endpoint assessment at the 120-day follow-up visit, participants in the sham-control group were offered to have their devices programmed to therapeutic stimulation.

The implant procedure and intraoperative multifidus contraction testing were completed under general anesthesia or intravenous sedation. A small incision was made over the L4 spinous process to facilitate lead placement. Under fluoroscopic guidance, the introducer needle was placed at the juncture of the L3 transverse process and the base of the L3 superior articular process, the location of the L2 medial branch of the dorsal ramus of the spinal nerve. Using a "modified Seldinger technique," a guide wire was placed through the needle, and after removal of the needle, a 7-French introducer was placed over the wire. The lead was then placed through the introducer. After correct lead placement was confirmed with anterior-posterior and lateral fluoroscopic views, the tines at the distal end of the lead were deployed on the anterior and posterior aspects of the intertransversari. At this point, electrical stimulation of the medial branch was performed, and contraction of the multifidi. confirmed by palpation. A pocket was then created for the

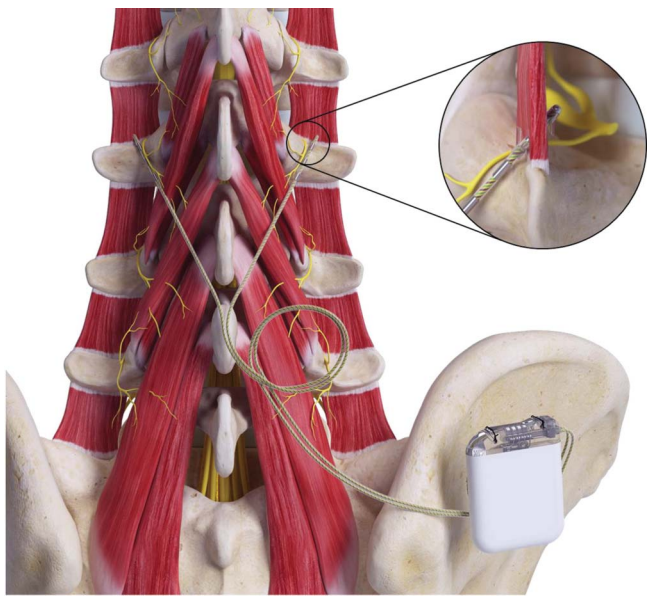


Figure 1. Implanted restorative neurostimulation system. The call-out shows the distal fixation tines deployed on the anterior and posterior aspects of the intertransversarii.

implantable pulse generator (IPG) in the gluteal or lower lumbar region, and the leads were tunneled subcutaneously to the pocket where they were connected directly to the IPG.

Device activation according to randomization assignment was scheduled approximately 14 days after the implant procedure to allow participants to recover from implant surgery. Programming was done by sponsor field clinical engineers and observed by the independent site observer. Devices of participants assigned to therapeutic stimulation were programmed to a stimulation frequency of 20 Hz, a pulse width of 214 μs, and participant-specific pulse amplitudes and electrode configurations to elicit tonic multifidus contractions for 10 seconds twice per minute during the stimulation session. Devices of participants assigned to sham (low-level) stimulation were programmed to unipolar stimulation from the most proximal electrode on the lead ipsilateral to the location of the IPG with 4 stimulation pulses of 0.4 mA and 31 μs to measure impedance at the initiation and 3 stimulation pulses of 0.1 mA and 31 μs delivered every two minutes during the stimulation session. All participants were instructed and trained to deliver two 30-minute stimulation sessions per day while in prone or side-laying position using their wireless activator.

2.5. Outcomes

Through 120-days, all reported outcomes were randomized and blinded, and after 120-days, all reported outcomes were unblinded and all participants were receiving therapeutic stimulation.

2.5.1. Primary outcome at 120 days

The composite primary endpoint was the difference in proportions of responders in the treatment and sham-control groups at 120 days post-randomization. A responder was defined as a participant who responded with ≥30% reduction from baseline in 7-day recall of average LBP-VAS score without an increase in baseline pain medications.

2.5.2. Secondary analysis of the primary outcome data

Prespecified secondary analysis of the primary outcome data included between-group differences in LBP-VAS at the 120-day assessment visit, a review of participants with increased analgesics, and a cumulative-proportion-of-responder analysis (CPRA). The CPRA uses a comparison of ranks of the percentage of "responders" across the range of all possible response thresholds and allows the reader to compare treatment groups at any responder level. This analysis has greater statistical power than the comparison of proportions of the dichotomized primary outcome.[32,34,56,71,75]

2.5.3. Secondary and supporting outcomes

The secondary and supporting efficacy outcomes were used to evaluate between-group differences at the 120-day assessment visit. The secondary efficacy outcome measures were the ODI,[30] EuroQol quality-of-life survey (EQ-5D-5L) index,[45] percent-of-pain-relief (PPR), subject global impression of change (SGIC),[50] and LBP resolution (VAS ≤2.5 cm). Supporting efficacy outcome measures included the Treatment Satisfaction Questionnaire, which asked participants "Are you satisfied with the outcome of your treatment?" with possible answers "Definitely yes," "Maybe," and "Definitely not," clinical global impression (CGI) of change,[40] and analgesics consumption.

After the blinded phase and primary endpoint assessment and starting therapeutic stimulation in the control group, these same outcome measures were assessed and compared with baseline out to 1 year.

2.5.4. Safety assessments

The primary safety assessment was of device- or procedure-related serious adverse events (SAEs) in participants at 120 days and supporting safety analysis continued through 1 year. All adverse events were actively solicited at each visit and documented throughout the trial and reported and coded according to the Medical Dictionary for Regulatory Activities, version 19.1. The independent CEC adjudicated all adverse events.

2.5.5. Pain medication

Participants were required to keep analgesic use stable through 120 days to avoid the risk of confounding the primary endpoint. After that, changes or adjustments were permitted. An increase in medications for LBP was defined as new medications added or any increase in daily dose. All medication changes were actively solicited at each visit and documented throughout the trial.

2.5.6. Sample size

The primary hypothesis was that the proportion of responders in the treatment group would be greater than that in the sham-control group. The initial sample size was determined assuming an expected responder proportion of 50% in the treatment group and 25% in the sham-control group, a 2-sided type-1 error rate of 0.05, and a minimum power of 80%. Under these assumptions, a total of 116 evaluable participants were required to detect the specified difference. The initial sample size was increased by 10% to 128 to allow for attrition. A single interim analysis was planned and performed when 50% (58/116) of the original planned study enrollment had completed the 120-day visit. Sample size re-estimation was based on conditional power following the method of Cui et al.[14] and was performed by a third-party independent statistician under the direction of the DMC. The DMC reviewed the results and recommended that, to maintain adequate power, a minimum of 168 participants be enrolled with additional participants to account for attrition, inherent variability, and the small sample size at the time of the interim analysis. The sponsor and all study personnel remained blinded to the results of the interim analysis to prevent introduction of operational bias.

2.6. Statistical analysis

Analysis of primary outcomes was done in the intention-to-treat (ITT) cohort, and a completers analysis was prespecified for secondary outcomes at 120 days. The difference in responder proportions (primary endpoint) was tested using a Wald asymptotic 2-sided binomial test for a difference in proportions with multiple imputation to handle missing values. The objective would be met if a statistically significant difference favoring the treatment group was found. The CPRA was conducted with the ITT primary endpoint data and used Friedman regression analysis with multiple imputation to handle missing values.

Continuous variables were summarized with means and SDs, and binary outcomes were represented as proportions. Differences between the treatment and sham-control groups were

presented with corresponding 95% confidence intervals (CIs). A *P*-value <0.05 was considered statistically significant.

All statistical analyses were prespecified in a detailed statistical analysis plan and conducted using SAS version 9.3 or later (SAS Institute Inc, Cary, NC) by independent biostatisticians. The study is registered on clinicaltrials.gov with identifier NCT02577354.

2.7. Role of the funding source

Mainstay Medical sponsored the study and contributed to study design; site selection; trial management; data collection; data analysis and interpretation (after unblinding of all participants); preparation, review, and approval of the manuscript. After unblinding of all participants, all authors had unrestricted access to study data. The corresponding author (overall principal investigator) wrote the first draft of the manuscript and all authors had final responsibility for submission.

3. Results

3.1. Study population

Participants were recruited between October 2016 and July 2018. Of 561 candidates screened for eligibility, 317 did not meet the criteria or declined to participate, 34 withdrew voluntarily, and 6 were excluded for noncompliance before implant. All participants had provided written informed consent.

A total of 204 participants underwent implantation and subsequent randomization with 102 assigned to therapeutic stimulation and 102 to sham stimulation. Participant disposition is provided in **Figure 2**.

Demographic and baseline characteristics were balanced between the 2 groups (**Table 1**). Participants in the trial had a mean age of 47 ± 9 years and 54% were women. Mean duration of CLBP was 14 ± 11 years from the onset of the first occurrence and the mean percentage of days with LBP in the prior year was 97 ± 8%. Mean VAS was 7.3 ± 0.7 cm, mean ODI was 39 ± 10, and the mean EQ-5D-5L index was 0.585 ± 0.174. All participants had undergone physical therapy with on average 31 ± 52 sessions. Of all participants, 12% had undergone medial branch rhizotomy (>1 year prior to enrollment), 49% had received spinal injections (>30 days prior to enrollment), and 37% were taking opioid analgesics for LBP.

3.2. Participant disposition

Three participants (2 treatment and 1 control) did not respond to visit scheduling requests and were permanently lost to follow-up before the 120-day visit requiring imputation of primary endpoint data. Four participants, all in the sham-control group, were permanently explanted after infection before the 120-day visit and consequently counted as nonresponders. For secondary outcomes, a completers analysis was prespecified, and baseline carried forward was used, thus counting these participants as failures for all analyses.

After the primary endpoint assessment, all participants in the sham-control group elected to receive therapeutic stimulation, and 1-year follow-up data were available for 176 participants (**Fig. 2**).

3.3. Primary endpoint at 120 days

The between-group difference in proportion of participants who achieved ≥30% LBP-VAS improvement without increase in analgesics was not statistically significant at 120 days (57.1% vs 46.6%; difference of 10.4%; 95% CI −3.3% to 24.1%; $P = 0.138$; **Table 2**).

3.4. Secondary analysis of the primary outcome data

The mean group difference in VAS improvement (−3.3 vs −2.4; difference of −0.9 cm; 95% CI −1.6 to −0.1 cm; $P = 0.032$; **Fig. 3**) was significant in favor of the treatment.

Eighteen participants increased analgesics, 9 in each group. In 6 cases, all of which were in the treatment group, the increase in analgesics was unrelated to LBP. Reasons for increased analgesics in these 6 cases were an ankle fracture, a tooth extraction, an upper respiratory tract infection, an anal abscess, a knee injury, and a renal stone.

The cumulative-proportion-of-responders analysis of the primary outcome data showed that across all possible response thresholds, treatment was superior to sham-control ($P = 0.0499$; **Fig. 4**).

3.5. Secondary endpoints at 120 days

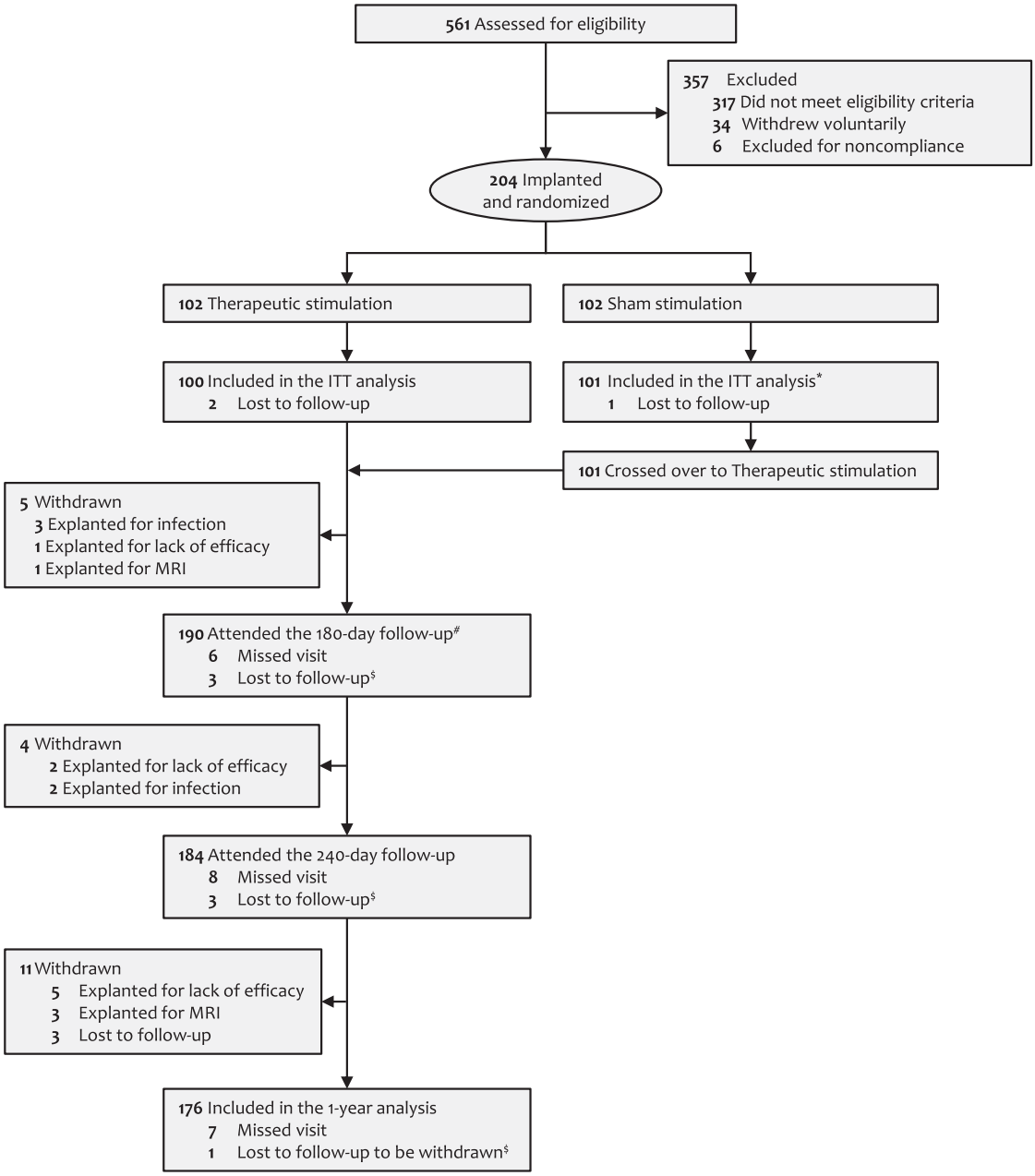
The first 4 of 5 secondary endpoints were statistically significant in favor of the treatment (**Table 2**): ODI (−17.5 vs −12.2; difference of −5.4 points; 95% CI −9.5 to −1.2 points; $P = 0.011$), EQ-5D-5L index (0.186 vs 0.115; difference of 0.071; 95% CI 0.018 to 0.123; $P = 0.009$), PPR (51.7% vs 35.0%; difference of 16.8%; 95% CI 7.3 to 26.3; $P < 0.001$), and proportion of participants for whom SGIC was "better" or "much better" (54.0% vs 33.7%; difference of 20.3%; 95% CI 6.9% to 33.8%; $P = 0.004$). Only the difference in proportion of LBP-resolution (VAS ≤ 2.5 cm) was not significant (34.0% vs 27.7%; difference of 6.3%; 95% CI −6.5% to 19.0%; $P = 0.335$). Because the primary endpoint did not meet statistical significance, hypotheses for secondary endpoints were not formally tested; therefore, these analyses were not adjusted for multiple comparisons. *P*-values are provided for descriptive purposes only.

3.6. Supporting endpoints at 120 days

The between-group differences in proportions of participants for whom CGI was "Much better" (57.0 vs 22.0; difference of 35.0%; 95% CI 22.3% to 47.7%; $P < 0.001$) and for whom treatment satisfaction questionnaire was "Definitely satisfied" (61.0 vs 39.6; difference of 21.4%; 95% CI 7.9% to 34.9%; $P = 0.002$) were also significant in favor of treatment (**Table 2**).

3.7. Blinding assessment at 120 days

In the treatment group, 59% guessed their assignment correctly, 14% guessed incorrectly, and 27% answered "Don't know." In the sham-control group, 44% guessed correctly, 24% guessed incorrectly, and 32% answered "Don't know." In the subgroup that correctly guessed their assignment (T guessing T, or C guessing C), the responder proportions were $P_{TT} = 71\%$ and $P_{CC} = 25\%$, respectively. For those who incorrectly guessed, they were $P_{TC} = 21\%$ and $P_{CT} = 83\%$, respectively, and for those answering "I don't know" (DK), responder proportions were $PT_{DK} = 44\%$ and $PC_{DK} = 50\%$, respectively. The James blinding index is 0.63 (95% CI 0.51 to 0.75), indicating blinding success.[53]



*4 explanted patients who attended the 120-day visit were counted as non-responders.
#1 patient did not complete the LBP VAS at this visit.
$3 patients lost to follow-up were not officially withdrawn until later in the study

Figure 2. CONSORT flow diagram for Participant Disposition.

3.8. Long-term outcomes after the double-blind phase

For participants who completed the 1-year follow-up (N = 176), efficacy outcomes consistently showed significant and clinically meaningful improvements compared with baseline in the combined cohort (all $P < 0.0001$; Table S2).[11,27,60,85] Mean average LBP had improved by −4.3 ± 2.6 cm (95% CI −4.7 to −3.9; $P < 0.0001$) or −58.9 ± 35.0% (95% CI −53.6% to −64.1%; $P < 0.0001$), and the proportion of participants with a 30% or greater improvement was 130/176 (74%); 64% of participants had a 50% or greater improvement and 52% reported LBP-resolution (LBP-VAS≤2.5 cm). Oswestry Disability Index had improved by −19.9 ± 15.8 (95% CI −22.3 to −17.6; $P < 0.0001$) or −50.5 ± 38.7% (95% CI −44.8 to −56.3; $P < 0.0001$), and the EQ-5D-5L index improved by 0.198 ± 0.207 (95% CI 0.167 to 0.229; $P < 0.0001$). Mean PPR was 65.7 ± 32.5%, and SGIC was "Better" or Much better" in 72%. Treatment satisfaction questionnaire was answered as "Definitely satisfied" in 78% of participants and CGI was "Much better" in 73%. Of 65/176 (37%) participants on opioids at baseline, 18/65 (28%) had discontinued their use.

3.9. Safety analysis

Eight device- or procedure-related SAEs were reported in 8 participants (4%), all before the 120-day follow-up (**Table 3**). Six

Table 1

Key characteristics of the study population at baseline.

Characteristic	Treatment group (N = 102), mean ± SD or n/N (%)	Control group (N = 102), mean ± SD or n/N (%)
Age (y)	46 ± 10	48 ± 9
Female sex	56/102 (55)	54/102 (53)
Body mass index (BMI)*	28 ± 4	28 ± 4
Pain duration from onset of the first occurrence (y)	14.4 ± 10.8	13.9 ± 10.4
Percent of days with low back pain in the past year	97 ± 8	97 ± 8
Leg pain associated with back pain	28/102 (27)	25/102 (25)
Previous medial branch rhizotomy	8/102 (8)	17/102 (17)
Months from most recent rhizotomy	62.7 ± 126.5	35.8 ± 33.5
Previous injection procedure	53/102 (52)	46/102 (45)
No. of prior physical therapy sessions	30 ± 39	32 ± 63
Medications for low back pain		
At least one medication for low back pain	77/102 (75)	85/102 (83)
NSAIDs	48/102 (47)	50/102 (49)
Opioid analgesics	36/102 (35)	40/102 (39)
Simple analgesics	24/102 (24)	18/102 (18)
Muscle relaxants	6/102 (6)	10/102 (10)
Anticonvulsants	6/102 (6)	12/102 (12)
Other (5% or lower)	14/102 (14)	10/102 (10)
VAS score for low back pain†	7.3 ± 0.7	7.2 ± 0.7
ODI score‡	40 ± 10	38 ± 10
EQ-5D-5L index§	0.572 ± 0.182	0.598 ± 0.165

* The body mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
† Scores on the visual analogue scales (VAS) for average recall low back pain over past 7 days range from 0 to 10, with higher scores indicating more severe pain.
‡ Scores on the Oswestry Disability Index (ODI) range from 0 to 100, with higher scores indicating more severe disability.
§ Scores on the European Quality of Life with 5 Dimensions and 5 Levels (EQ-5D-5L) index range from −0.5 to 1, with higher scores indicating better quality of life.

participants developed a pocket infection, which all resolved after system explant and antibiotics. In one participant, a new system was implanted before the 120-day visit after the infection had cleared. One participant had an intraoperative upper airway obstruction that resolved, and one participant developed an ongoing nonradicular patch of numbness on the surface of his thigh. No additional serious device- or procedure-related events were reported through the 1-year visit and no lead migrations were observed. Seven unrelated SAEs were reported in 7/204 (3%) participants, and all events were reviewed by the CEC and adjudicated as unrelated.

Including the above, a total of 27 participants (13%) underwent a total of 30 surgical interventions during which 19 systems were explanted (9%), one system reimplanted (<1%), 4 pulse generators repositioned (2%), and 6 participants had their leads replaced (3%). Reasons for explant were lack of effectiveness (9), infection (6), and safety precaution before MRI scan (4).

Table S3 summarizes all device- or procedure-related adverse events through 1 year. Most of these events occurred within the first 30 days and were generally procedure-related.

4. Discussion

The objective of this trial was to determine the safety and efficacy of restorative neurostimulation in patients with refractory mechanical CLBP despite at least >90 days of medical management, which included at least medication and physical therapy prescribed for CLBP. The primary endpoint of this randomized sham-controlled trial was inconclusive in terms of treatment superiority; that is, it did not meet statistical significance but the CI is compatible with a clinically meaningful treatment effect.[2,38,62] The totality of data from the blinded phase was consistent with what can be considered a modest, clinically meaningful treatment benefit at 120 days. The statistically significant between-group differences for pain intensity (VAS) and disability (ODI) with standardized response means of 0.30 and 0.36, respectively, are modest treatment effect sizes consistent with those for existing efficacious treatments for chronic pain.[76,78] Improvements from baseline, which continued to accrue in all outcome measures after conclusion of the double-blind phase, were clinically important at 1 year, and the incidence of serious procedure- or device-related adverse events compared favorably with the literature for other neuromodulation therapies for chronic pain.

4.1. Interpretation of results

Even when a primary endpoint is inconclusive, secondary findings and safety outcomes may be compelling enough to affect regulatory approvals and clinical practice,[38] especially for patients in whom available treatment options are not effective. We believe that the reported findings merit interpretation within this context, which includes that the results from this trial informed FDA Premarket Approval and the listing on the Australian Register of Therapeutic Goods.

Responses to effective pain treatments are multidimensional,[25,83] and across most secondary and supporting endpoints at 120 days, the 95% CIs excluded zero and were consistent with a clinically meaningful treatment effect

Table 2

Outcomes for primary, secondary, and supporting endpoints at 120 days.

Endpoint or analysis	Baseline	120 Days			
	All (N = 204), mean ± SD	Treatment (N = 100), mean ± SD, n/N (%)	Sham control (N = 101), mean ± SD, n/N (%)	Between-group difference (95% CI)	*P*
Primary outcomes					
Responders ITT (%)		N = 102* (57.1)	N = 102* (46.6)	10.4 (−3.3 to 24.1)	0.138†
CPRA		N = 102*	N = 102*	NA	0.0499‡
LBP VAS (cm)	7.3 ± 0.7	4.0 ± 2.7	4.8 ± 2.9		
Secondary and supporting outcomes					
Change in VAS (cm)		−3.3 ± 2.7	−2.4 ± 2.9	−0.9 (−1.6 to −0.1)	0.032§
Change in VAS (%)		−44.6 ± 36.8	−33.3 ± 40.8	−11.2 (0.4 to 22.0)	0.042§
ODI	39.1 ± 10.3	22.3 ± 14.5	25.7 ± 15.0		
Change in ODI		−17.5 ± 15.1	−12.2 ± 14.6	−5.4 (−9.5 to −1.2)	0.011§
Change in ODI (%)		−43.0 ± 34.3	−31.2 ± 38.2	−11.8 (−21.9 to −1.7)	0.022§
EQ-5D-5L	0.585 ± 0.174	0.758 ± 0.160	0.713 ± 0.160‖		
Change in EQ-5D-5L		0.186 ± 0.199	0.115 ± 0.178‖	0.071 (0.018 to 0.123)	0.009§
PPR (%)		51.7 ± 32.3	35.0 ± 35.8	16.8 (7.3 to 26.3)	<0.001§
SGIC "better" or "much better"		54/100 (54.0)	34/101 (33.7)	20.3 (6.9 to 33.8)	0.004¶
LBP resolution (VAS ≤ 2.5 cm)		34/100 (34.0)	28/101 (27.7)	6.3 (−6.5 to 19.0)	0.335¶
TSQ "definitely satisfied"		61/100 (61.0)	40/101 (39.6)	21.4 (7.9 to 34.9)	0.002¶
CGI "much better"		57/100 (57.0)	22/100 (22.0)	35.0 (22.3 to 47.7)	<0.001¶

* Results for 3 patients (2 treatment and 1 sham) lost to follow-up were included using multiple imputation.
† *P*-value based on a Wald asymptotic test of proportions with multiple imputation to handle missing values.
‡ *P*-value based on a Friedman regression analysis with multiple imputation to handle missing values.
§ *P*-value is from a 2-sample, 2-sided *t* test.
¶ *P*-value is from chi-square test for the categories defined in the first column.
‖ One patient in the sham-control group did not complete all sections of the EQ-5D-5L questionnaire; therefore, no score could be completed.
CI, confidence interval; CGI, clinician global impression; CPRA, cumulative proportion of responders analysis; ITT, intention-to-treat; LBP, low back pain; ODI, Oswestry Disability Index; SGIC, subject global impression of change; TSQ, treatment satisfaction questionnaire; VAS, visual analogue scale.

(**Table 2**).[12,24,26,35,41,67,76,78] The prespecified secondary CPRA of the ITT primary outcome data showed a significant separation across the range of possible responder thresholds, illustrating the adverse impact of information loss due to primary outcome dichotomization (**Fig. 4**).

Long-term outcomes for the combined cohort continued to improve after conclusion of the double-blind phase (Fig. S2). These results may be consistent with a mechanism that restores function in contrast to conventional neurostimulation, which produces analgesia as long as stimulation is delivered. One-year results show clinically substantial improvements compared with baseline (Table S2). Mean LBP-VAS had improved by 59% from "severe" to "mild,"[6] mean disability (ODI) by 51% from borderline "severe" to "minimal,"[31] and 28% of participants who were taking opioids at baseline had eliminated them. Compared to baseline, 73% of participants had an improvement of ≥50% in VAS and/or ODI and 50% of participants in both VAS and ODI.

Considering the long history of CLBP and the consistency and severity of symptoms, it seems unlikely that either a placebo response or variability in the natural course of CLBP could account for the observed results; that is, a modest but clinically meaningful benefit at 120 days that increased over time through 1 year.[9,13,23,52]

The incidence of device- and procedure-related SAEs, all before the 120-day follow-up visit, was 8/204 (3.9%, **Table 3**), including 6 pocket infections requiring system removal. This compares favorably with SAE incidence data published for other neuromodulation therapies for chronic pain.[28,44] The system removal rate of 19/204 (9.3%) is in line with that reported for spinal cord stimulation over the same period.[42,86] In contrast to spinal cord stimulation, leads are placed outside of the spinal canal, thereby avoiding risk of spinal cord injuries. Lead migration represents the most common adverse event reported in neurostimulation trials, occurring at rates of 1.4% to 13.6%.[19,44] No lead migrations were observed in this trial, demonstrating the effectiveness of the proprietary distal fixation tines.

4.2. Important considerations

Time-to-effect and the duration-of-effect have a significant impact on outcomes.[75] Analgesic treatments such as opioids or spinal cord stimulation exhibit a relatively immediate time-to-effect (seconds to hours) upon administration or activation, and a relatively short duration-of-effect after cessation. By

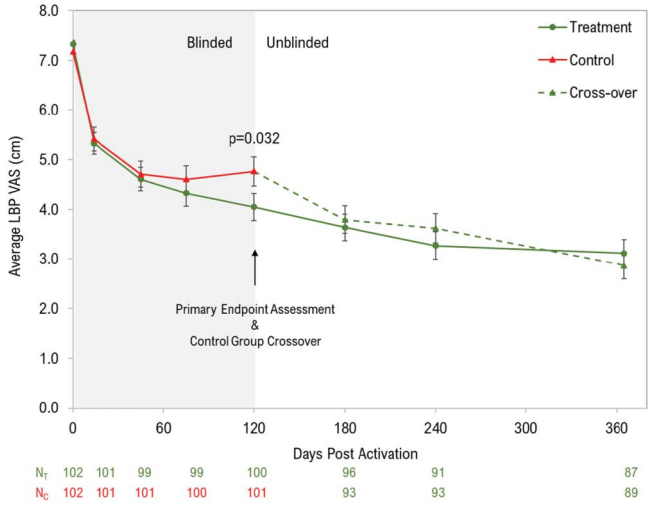


Figure 3. Low back pain-VAS trajectory. Reduction in average LBP-VAS shows a significant mean group difference at 120 days ($P = 0.032$) and improvements in CLBP continue to accrue through 1 year. CLBP, chronic low back pain; VAS, visual analogue scale.

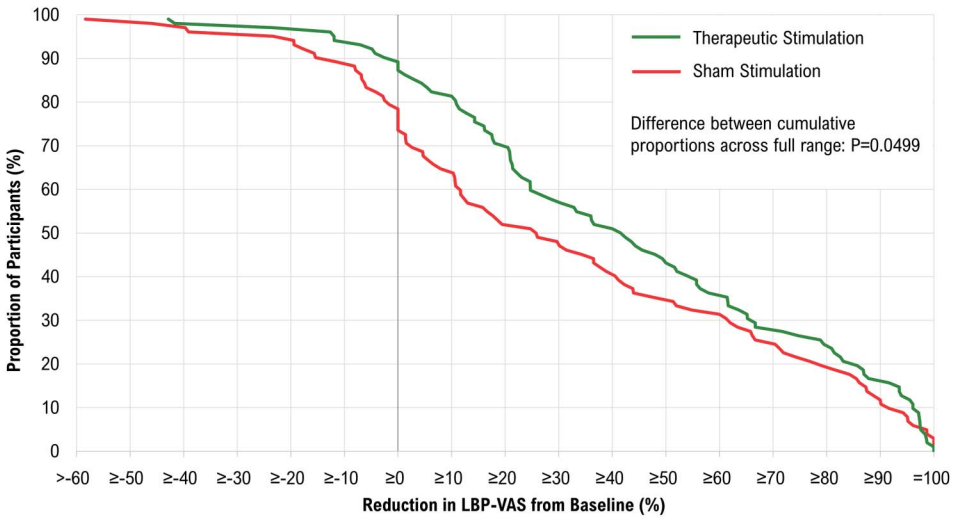


Figure 4. Primary outcome analysis. Proportion of participants with an improvement in LBP-VAS of ≥30% and no increase in analgesics ($P = 0.138$). Comparison of the cumulative proportion of responders shows significant separation (area between the curves) in favor of the treatment ($P < 0.0499$). This prespecified analysis was conducted with the primary endpoint and used Friedman regression analysis with multiple imputation to handle missing values, which is a comparison of ranks that preserves information over an endpoint based on dichotomization, thereby improving statistical power. LBP-VAS, low back pain visual analogue scale.

contrast, restorative neurostimulation studied in this trial involves mechanisms with a longer time to maximum impact. It may take several months for a meaningful improvement on pain and function to accrue, but once attained, the effect can be durable. This leads to several important considerations that inform interpretation of the observed results and the design of future trials:

4.2.1. Impact of dichotomization

The dichotomized endpoint uses a fixed threshold to determine whether a participant is a responder at 120 days or not. As such, it does not acknowledge ongoing progress towards the maximum treatment effect, which many participants will only reach well beyond 120 days. The CPRA presents all possible thresholds of response, not just one, and therefore is much more informative. As it weighs all levels of response along the recovery trajectory in both groups, it may be a more appropriate primary outcome in clinical trials of restorative or rehabilitative treatments such as this one.[32,56,77]

4.2.2. Impact of primary outcome

Pain intensity and disability are interdependent symptoms of the underlying condition and codeterminants of a patient's perception of well-being or health state.[25] A composite primary endpoint of pain and function as proposed by Patel et al.[61] might have more completely captured the clinically meaningful treatment benefits at the 120-day timepoint. A hypothesis generating post hoc analysis of such a composite endpoint (ie, 30% improvement in VAS or ODI, no worsening in either, and no increase in pain medication) showed responder rates of 70% vs 49% ($P = 0.003$).

4.2.3. Impact of duration of sham response

Although the short-term sham response of surgery and other invasive procedures are understood to be relatively immediate and large, particularly in the field of pain-related procedures,[39] less is known about their long-term sham response. Although surgical sham effects can linger, we consider it unlikely for a sham response to follow a trajectory of ongoing accrual of improvements in all outcome measures through 1 year. In this trial, the rapid sham response seemed to peak and reverse at approximately 3 months at around the same time the accumulating treatment effect was becoming statistically significant and clinically meaningful. This suggests that a longer blinded phase of the trial might have allowed further benefit accrual in the treatment arm and confirmation of response reversal in the sham-control arm. For future clinical trials, employment of a nonactive sham (ie, no stimulation) can be considered to mitigate the unlikely potential of therapeutic effectiveness of sham stimulation.

Table 3

Device- and procedure-related serious adverse events and surgical interventions.

	Events, n	Subjects, n/N (%)
Device- and procedure-related SAEs	8	8/204 (3.9)
Infection (resolved)	6	6/204 (2.9)
Intraprocedural upper airway obstruction (resolved)	1	1/204 (0.5)
Nonradicular patch of numbness on thigh (ongoing)	1	1/204 (0.5)
Surgical interventions and reasons*	30	27/204 (13.2)
System removal	19	19/204 (9.3)
Reported lack of effectiveness	9	9/204 (4.4)
Infection†	6	6/204 (2.9)
Facilitate MRI	4	4/204 (2.0)
Revision	10	10/204 (4.9)
Lead replacement	6	6/204 (2.9)
Pulse generator repositioning	4	4/204 (2.0)
Reimplant postinfection†	1	1/204 (0.5)

* Patients may have had more than one procedure; therefore, the total does not equal the sum of the categories.
† One patient was reimplanted after the infection cleared.
SAEs, serious adverse events. MRI, magnetic resonance imaging.

4.2.4. Impact of postoperative instructions

Instructions by implanting physicians to avoid strenuous activities to reduce the risk of lead migration may have led to unintentional bias against the treatment. Because the distal anchoring tines effectively mitigate the risk of early lead migration, recommending an early return to regular activity might have favored the treatment arm.

Although these considerations inform future trial designs of restorative neurostimulation for CLBP, several practical limitations remain or have emerged. A prolonged, sham-controlled, parallel-arm trial (eg, 1 or more years) may impact participant recruitment, complicate treatment compliance and blinding, and raise ethical questions about undue withholding of a presumed effective treatment. Furthermore, participant blinding will become increasingly difficult to maintain as more information about the therapy is becoming publicly available. Finally, commercial availability of the system has provided patient access to the therapy.

4.3. Strengths and weaknesses

This trial has several strengths. To the best of our knowledge, this is the first sham-controlled, double-blinded trial of an implantable neurostimulator for CLBP that is consistent with the rigor described in the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials emerging quality standards for neuromodulation trials.[51,54,57] In addition to the use of an active sham, a parallel-group design and postimplant randomization, several rigorous measures were imposed to ensure the integrity of blinding and equipoise through primary endpoint assessment at 120 days. Given the complexity of blinding in this sham-controlled trial, blinding was maintained relatively well. From the data, it seems that correct assignment guesses were informed by perceived benefit or lack thereof. Especially in placebo- or sham-controlled trials, this cannot be prevented and will lead to a higher proportion of participants correctly guessing their assignment when a therapy is effective without necessarily indicating that the blinding was broken.[69,70] The James blinding index,[53] which acknowledges this reality, indicated blinding success (James blinding index: 0.63; 95% CI 0.51 to 0.75).

Several limitations need to be considered when interpreting the results of this trial. First, at the time of trial design, the size and duration of the sham response to this type of treatment in participants with CLBP was unknown. The statistical design assumptions, derived from a literature review for available CLBP treatments, underestimated the response to a surgically implanted active sham device. Although the LBP-VAS trajectory suggests that the sham effect may be reversing at 120 days (**Fig. 4**), due to the prespecified switch of the sham-control group to therapeutic stimulation, we were unable to confirm this longer term. Second, although previous studies had shown that observed improvements with this rehabilitative treatment accrue over time,[18] endpoint timing was set to 120 days for practical and ethical reasons, and the fixed 30% threshold for pain relief reflected the expected improvement at 120 days rather than the fully accrued long-term treatment effect. Finally, although sham stimulation parameters were set to low amplitude and frequency values, a potential therapeutic effect cannot be ruled out and this might have diminished the magnitude of the group differences in the outcome measures.

5. Conclusion

In conclusion, this double-blind, randomized, sham-controlled trial provided important insights and design considerations for future neuromodulation trials. Although the primary endpoint was inconclusive, overall data from the blinded phase of this trial are consistent with a clinically meaningful benefit at 120 days. After unblinding and the switch from sham to therapeutic stimulation in the sham-control group, improvements increased over time out to 1 year in the combined cohort. The incidence of serious procedure- or device-related adverse events compared favorably with rates published for other neuromodulation therapies for chronic pain. Follow-up of participants in this trial will continue for a total of 5 years, providing additional insights into the long-term benefits, risks, and reliability of this device.

Conflict of interest statement

Mainstay Medical funded this pivotal regulatory trial and paid all investigators either directly or indirectly (payment to investigator employer). Trial agreements covering participant medical costs related to the trial were in place with all institutions. Travel expenses related to investigator meetings and training were reimbursed only with prior authorization.

All authors use the automated ICMJE Form for Disclosure of Potential Conflicts of Interest to generate their disclosure statements:

Study investigators: C. Gilligan discloses that Mainstay Medical pays part of his salary directly to his department. M. Russo reports personal fees from Mainstay Medical, outside the submitted work. M. Green reports other from Mainstay Medical, during the conduct of the study. C. Gilmore reports personal fees and other from SPR Therapeutics; personal fees from Nevro; personal fees from Abbott Neuromodulation; and personal fees from Medtronic Neuromodulation, outside the submitted work. V. Mehta is chief investigator in an ongoing investigator-initiated trial funded by Mainstay Medical and has received travel support to present in meetings from Mainstay Medical. K. Deckers served as a principal investigator for the trial described in this manuscript and received compensation as principal investigator from Mainstay Medical. K. De Smedt reports other from Mainstay Medical, during the conduct of the study, and personal fees from Mainstay Medical, outside the submitted work. U. Latif reports personal fees from Medtronic, outside the submitted work. P. Georgius reports personal fees from Boston Scientific, personal fees from Abbott, and personal fees from Spectrum Therapeutics, outside the submitted work. F. Huygen reports grants from Mainstay, during the conduct of the study; grants and personal fees from Abbott; grants and personal fees from the Saluda Advisory Board; and nonfinancial support from the Boston Scientific Advisory Board, outside the submitted work. G. Baranidharan reports grants and personal fees from Nevro Corporation, grants and personal fees from Abbott, grants and personal fees from Boston Scientific, and personal fees from Nalu Medical, outside the submitted work. V. Patel reports grants from Mainstay, during the conduct of the study, grants from Orthofix, grants from Pfizer, grants from Premia Spine, grants from Medicrea, grants from Globus, and grants from Aesculap, outside the submitted work. E. Ross reports personal fees and other from Mainstay Medical, during the conduct of this study. A. Carayannopoulos does not believe he has any conflicts of interest that would unduly influence him in participation nor in manuscript preparation/coauthorship. S. Hayek reports grants from Mainstay Medical during the conduct of the study. A. Gulve reports nonfinancial support from James Cook University Hospital, Middlesbrough; grants and nonfinancial support from Mainstay Medical International PLC; personal fees from Medtronic; grants and personal fees from Nevro; grants and personal fees from

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Committee members: W. Klemme reports personal fees from Mainstay Medical, Inc, during the conduct of the study. J. Rathmell reports personal fees from Mainstay Medical during the conduct of the study, personal fees from the American Board of Anesthesiology, and personal fees from American Society of Anesthesiology, outside the submitted work. R. Levy is a consultant for Abbott, Saluda, Nalu, and Mainstay Medical. He has stock options <5% from Nalu and Saluda. J.P. Heemels is employee of Mainstay Medical. The remaining authors have no conflicts of interest to disclose.

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