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Five-Year Longitudinal Follow-up of Restorative Neurostimulation Shows Durability of Effectiveness in Patients With Refractory Chronic Low Back Pain Associated With Multifidus Muscle Dysfunction

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ABSTRACT

Background: Adults with refractory, mechanical chronic low back pain associated with impaired neuromuscular control of the lumbar multifidus muscle have few treatment options that provide long-term clinical benefit. This study hypothesized that restorative neurostimulation, a rehabilitative treatment that activates the lumbar multifidus muscles to overcome underlying dysfunction, is safe and provides relevant and durable clinical benefit to patients with this specific etiology.

Materials and Methods: In this prospective five-year longitudinal follow-up of the ReActiv8-B pivotal trial, participants ($N = 204$) had activity-limiting, moderate-to-severe, refractory, mechanical chronic low back pain, a positive prone instability test result indicating impaired multifidus muscle control, and no indications for spine surgery. Low back pain intensity (10-cm visual analog scale [VAS]), disability (Oswestry Disability Index), and quality of life (EuroQol's "EQ-5D-5L" index) were compared with baseline

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and following the intent-to-treat principle, with a supporting mixed-effects model for repeated measures that accounted for missing data.

Results: At five years ($n = 126$), low back pain VAS had improved from 7.3 to 2.4 cm (−4.9; 95% CI, −5.3 to −4.5 cm; $p < 0.0001$), and 71.8% of participants had a reduction of ≥50%. The Oswestry Disability Index improved from 39.1 to 16.5 (−22.7; 95% CI, −25.4 to −20.8; $p < 0.0001$), and 61.1% of participants had reduction of ≥20 points. The EQ-5D-5L index improved from 0.585 to 0.807 (0.231; 95% CI, 0.195–0.267; $p < 0.0001$). Although the mixed-effects model attenuated completed-case results, conclusions and statistical significance were maintained. Of 52 subjects who were on opioids at baseline and had a five-year visit, 46% discontinued, and 23% decreased intake. The safety profile compared favorably with neurostimulator treatments for other types of back pain. No lead migrations were observed.

Conclusion: Over a five-year period, restorative neurostimulation provided clinically substantial and durable benefits with a favorable safety profile in patients with refractory chronic low back pain associated with multifidus muscle dysfunction.

Clinical Trial Registration: The Clinicaltrials.gov registration number for the study is NCT02577354; registration date: October 15, 2016; principal investigator: Christopher Gilligan, MD, Brigham and Women's Hospital, Boston, MA, USA. The study was conducted in Australia (Broadmeadow, New South Wales; Noosa Heads, Queensland; Welland, South Australia; Clayton, Victoria), Belgium (Sint-Niklaas; Wilrijk), The Netherlands (Rotterdam), UK (Leeds, London, Middlesbrough), and USA (La Jolla, CA; Santa Monica, CA; Aurora, CO; Carmel, IN; Indianapolis, IN; Kansas City, KS; Boston, MA; Royal Oak, MI; Durham, NC; Winston-Salem, NC; Cleveland, OH; Providence, RI; Spartanburg, SC; Spokane, WA; Charleston, WV).

Keywords: Chronic low back pain, non-neuropathic pain, opioid reduction, peripheral nerve stimulation, restorative neurostimulation

INTRODUCTION

Functional instability of the lumbar spine and consequent mechanical chronic low back pain are typically symptoms of multifidus muscle dysfunction.[1,2] Affected patients very rarely experience spontaneous, substantial, or durable improvements in their pain or disability.[3,4]

Spine surgeries are typically not indicated unless imaging studies identify an etiology that is amenable to surgery.[5] Although available pharmaceutical, noninvasive, and invasive treatments provide relief and improved function for some, they remain ineffective or provide only transient relief for many. Nevertheless, patients with mechanical chronic low back pain use significant health care resources, including physical therapy, medication, and repeated palliative interventions.[6,7]

Given prevalence is highest in the working age population, indirect costs are driven disproportionately by diminished work performance and absenteeism. In particular, those with physical jobs may consequently leave the workforce and become reliant on government assistance.[8] Effective, durable therapies can therefore significantly affect the clinical and economic burden of chronic low back pain by reducing the need for long-term palliation in a relatively young patient cohort.[9]

The role of the multifidus muscle and the way its dysfunction leads to low back pain have been described in detail elsewhere.[1,2,10,11] In summary, the multifidus muscles are the most

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important stabilizers of the lumbar spine and play a crucial role in maintaining a pain-free range of motion, providing segmental stability in response to anticipated changes in posture, and protecting against sudden perturbations.[1,12–14] Injuries to spinal structures, such as the intervertebral discs or facet joints, can cause arthrogenic muscle inhibition and sustained neurologic dysfunction of the multifidus muscle around the painful joint(s). Consequently, the multifidus can no longer fulfil its protective function, and the spine becomes prone to repeat injury and chronic nociception during normal activities of daily living.[2]

A restorative or rehabilitative treatment that specifically addresses the underlying neuromuscular pathophysiology seems a prudent initial approach,[15] especially considering the limited effectiveness of available alternatives.[16,17] Restorative treatments, including targeted motor control exercises and restorative neurostimulation, aim to reactivate and reengage the deep multifidus muscles that normally protect the lumbar spine against painful excursions. However, results of motor control exercise programs targeting the multifidus muscle are mixed.[18,19] The deep muscle contractions needed to reverse impaired neuromuscular control are difficult to achieve voluntarily, especially in the presence of underlying inhibition and degeneration of the multifidus muscle.[1,20]

Restorative neurostimulation (ReActiv8®, Mainstay Medical, Dublin, Ireland) is indicated for patients with refractory, mechanical chronic low back pain associated with multifidus dysfunction[17,21] and no indications for spinal surgery.[22] The system stimulates the motor neurons of the L2 medial branch of the dorsal ramus to elicit episodic contractions of the multifidus muscle to overcome underlying inhibition and facilitate reengagement of the muscle in segmental stabilization.[2,11,23]

Although all implantable neurostimulation systems aim to provide long-term therapy, few prospective studies have reported follow-up data beyond one year. In this study, we report on the five-year outcomes of the pivotal trial that included adult patients experiencing refractory, disabling, mechanical chronic low back pain associated with multifidus dysfunction.

MATERIALS AND METHODS

Trial Design

ReActiv8-B was a prospective, parallel-group, randomized, double-blind, sham-controlled clinical trial in 26 centers in the USA, Australia, and Europe. A total of 204 participants were recruited, underwent implantation, and were randomized between October 2016 and July 2018. Details regarding patient eligibility, study design, implant procedure, and results through three years have been previously published.[23–25] Given all participants received therapeutic stimulation from four months onward, the annual follow-ups are a prospective, single-arm, open-label continuation of the pivotal trial.

Conduct of the trial complied with the Food and Drug Administration (FDA) regulations, International Organization for Standardization ISO14155, International Conference on Harmonization, and the Declaration of Helsinki. Local institutional review board or ethics committee approval was obtained at each site, and all participants provided written informed consent. Informed consent required participants to withdraw from the study if the device was explanted at any time for any reason, including resolution of pain. Results are reported in accordance with the Consolidated Standards of Reporting Trials guidelines.[26] Independent trial oversight included a clinical events committee, a data monitoring committee, and a magnetic resonance imaging review committee. The study was registered with clinicaltrials.gov on October 15, 2016 (NCT02577354; principal investigator: Christopher Gilligan, MD, Brigham and Women's Hospital, Boston, MA).

Participants

Study participants were adults (aged 22–75 years) with a diagnosis of moderate-to-severe, disabling, refractory, predominantly mechanical chronic low back pain (visual analog scale [VAS] between 6.0 and 9.0 cm on a 10-cm scale and Oswestry Disability Index [ODI] between 21 and 60 points on a 100-point scale) with pain on at least half of the days in the year before baseline. All participants had a positive prone instability test result (provoked nociceptive pain during posterior-anterior pressure on individual lumbar vertebrae that improves with activation of the posterior lumbar musculature) consistent with impaired neuromuscular control of the multifidus muscle and lumbar segmental instability.[17] Their chronic low back pain persisted despite a minimum of 90 days of conservative medical management that included at least medication and physical therapy, and they were not considered candidates for spine surgery. Eligibility criteria have been discussed in more detail elsewhere.[27]

Procedures

The proposed restorative mechanism of action depends on isolated activation of the lumbar multifidus muscles.[1,20] Owing to the polysegmental innervation of the multifidi, the aim is to evoke the most consistent multifidus contractions to cover most of the muscle group from below the level of stimulation.[28,29] During the implant procedure, leads were placed bilaterally 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 innervating the multifidus (Fig. 1). An intraoperative trial confirmed contraction of the multifidi in response to electrical stimulation of the medial branch.

During the open-label phase of the study, all devices were programmed to deliver therapeutic stimulation at a frequency of 20 Hz, a pulse width of 214 μs, and participant-specific pulse amplitudes and electrode configurations to elicit strong multifidus contractions for 10 seconds twice per minute. Participants were instructed and trained to deliver two 30-minute stimulation sessions per day while prone or lying on their side, using their wireless activator. The device recorded participant usage and did not permit >60 minutes of stimulation in a 24-hour period.

Outcome Measures

Low back pain intensity was assessed on a VAS ranging from 0 (no pain) to 10 (worst pain imaginable),[30] Functional impact (ie, disability) was assessed using the ODI questionnaire,[31] and health-related quality of life with the EuroQol EQ-5D-5L questionnaire.[32] Additional outcome measures included percent pain relief, subject global impression of change,[33] low back pain resolution (residual VAS of ≤2.5 cm), treatment satisfaction, clinical global impression,[34] and patient-reported intake of pain medication. All outcomes were assessed and compared with baseline at one, two, three, four and five years.

Ongoing safety reporting included serious device- or procedure-related adverse events, which were actively solicited and documented at each visit, reported, and coded according to the Medical Dictionary for Regulatory Activities, version 19.1. The clinical events committee adjudicated all adverse events.

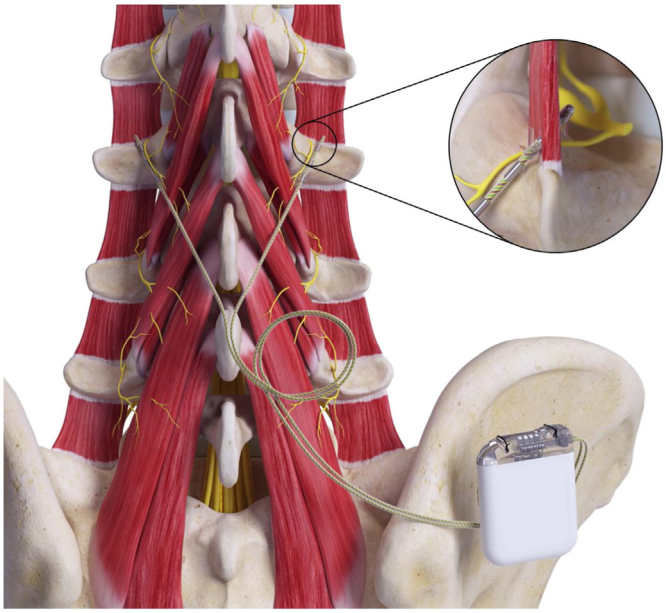

Figure 1. Implanted restorative neurostimulation system. The inset picture shows the distal fixation tines deployed on the anterior and posterior aspects of the intertransversarii and the electrode positioning adjacent to the medial branch of the dorsal ramus.

Statistical Analysis and Reporting

Completers Analysis

The prespecified analysis provides descriptive statistics and response proportions for all outcome measures among completers. Descriptive statistics, including mean and SD or SE of the mean and 95% CIs, were used to summarize continuous variables. Binary outcomes were represented as counts and proportions.

Sporadically, participant-reported data were incomplete. Denominators represent the number of participants for whom the data were available.

In addition to statistical significance, throughout this study, we provide context of clinical importance by reporting responder proportions at various thresholds. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials made recommendations for the interpretation of the clinical importance of treatment outcomes in chronic pain clinical trials: Improvements of 10% to 20% in VAS are considered clinically "minimally important;" improvements of ≥30% are considered clinically "moderately important" or "much improved," and improvements of ≥50% are considered clinically "substantial" or "very much improved."[35,36] Similar thresholds have been defined for the ODI, with absolute changes of ≥5 to 10 points considered clinically "minimally important," 15 points "moderately important," and ≥20 points "substantial."[37,38]

Intent-to-Treat Analysis

Over a five-year follow-up period, neurostimulation studies are inherently affected by participant attrition and missing data. To help assess the robustness of the findings, we have chosen to complement the completers analysis with a supplemental analysis that follows the intent-to-treat principle ($N = 204$) and uses principled methods for handling missing data.

All participants who underwent system removal for any reason, including resolution of pain, were withdrawn from the study, typically within 30 days after explant. For participants who requested system removal because the therapy did not meet their expectations or those with postimplant infection, baseline observation carried forward was used to account for missing data. This approach is consistent with the "hypothetical approach" described in FDA Guidance E9 (R1) that subjects withdrawn owing to inadequate response are treated as though they have minimal improvements.[39] Outcomes for subjects withdrawn or lost to follow-up for other reasons were assumed to be missing at random (Table 1). The missing-at-random assumption is that conditional on observed data over time, the likelihood of missingness is independent from the distribution of the unobserved outcome. Mixed-effects models for repeated measures were used to provide implicit imputations of these missing data.[40,41] Under the missing-at-random assumption, mixed-effects models for repeated measures provide a robust longitudinal likelihood-based data analysis, which uses the correlations over time to produce unbiased estimates of outcomes.[42] The missing-at-random assumption is tenable after application of baseline observation carried forward as previously described. The validity of the missing-at-random assumption was evaluated by comparing the trajectory of the cohort with that of the completer cohort.

To evaluate mean changes from baseline, 95% CIs and adjusted paired *t*-tests derived from mixed-effects models for repeated contrasts were used. Two-sided p values < 0.05 were considered statistically significant, with no adjustment for multiplicity.

To estimate the proportion of subjects achieving "success" for the defined binary outcome variables, mixed-effects models for repeated measures were used for overall estimates of success by visit with associated 95% confidence limits after applying baseline observation carried forward for subjects missing owing to inadequate pain relief or device removal due to infection.[40]

Analyses were performed by third party statisticians using SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Study Population

Demographic and baseline characteristics of the 204 participants are listed in Table 2. Participants had a mean age of 47 ± 9 years, and 54% were female. Mean duration of chronic low back pain was 14 ± 11 years from the onset of the first occurrence, and the mean percentage of days with low back pain in the previous year was 97% ± 8%. Mean VAS was 7.3 ± 0.7 cm; the mean ODI was 39.1 ± 10.3, and mean EQ-5D-5L index was 0.585 ± 0.174. All participants had undergone physical therapy with an average of 31 ± 52 sessions; 12% had undergone medial branch rhizotomy (all ≥one year before enrollment); 49% had received spinal injections (all ≥30 days before enrollment); and 37% were taking opioid analgesics for low back pain.

Participant Disposition

The number of participants who provided data during the annual follow-ups (complete cases) was 176 (86%), 156 (76%), 133 (65%), 119 (58%), and 126 (62%) for years 1 through 5, respectively.

Over the five-year study duration, 62 participants had explants for various reasons. Notably, 18 participants elected to have their devices removed for resolution of their pain symptoms after

Table 1. Key Characteristics of the Study Population at Baseline.

Characteristic	All participants (N = 204) Mean ± SD or n/N (%)
Age (y)	47 ± 9
Female sex	110/204 (54)
BMI (kg/m^2)	28 ± 4
Pain duration from onset of the first occurrence (y)	14.2 ± 10.6
Percent of days with low back pain in the previous y	97 ± 8
Leg pain associated with back pain	53/204 (26)
Previous medial branch rhizotomy	25/204 (12)
Months from most recent rhizotomy	44.4 ± 74.7
Previous injection procedure	99/204 (49)
No. of previous injections	2.6 ± 52
Previous physical therapy	204/204 (100)
No. of physical therapy sessions	31 ± 52
Medications for low back pain	
≥1 medication for low back pain	160/204 (78)
NSAIDs	98/204 (48)
Opioid analgesics	76/204 (37)
Simple analgesics	42/204 (21)
Muscle relaxants	16/204 (8)
Anticonvulsants	18/204 (9)
Other (≤5%)	24/204 (11)
VAS score for low back pain (cm)*	7.3 ± 0.7
ODI score†	39.1 ± 10.3
EQ-5D-L index‡	0.585 ± 0.174
Positive Prone Instability Test (L1–L5)	204/204 (100%)
L1 positive	13/204 (6%)
L2 positive	46/204 (23%)
L3 positive	98/204 (48%)
L4 positive	144/204 (71%)
L5 positive	97/204 (48%)
5 adjacent positive levels (L1–L5)	2/204 (1%)
4 adjacent positive levels (L2–L5)	6/204 (3%)
3 adjacent positive levels	30/204 (15%)
3 nonadjacent positive levels	6/204 (3%)
2 adjacent positive levels	85/204 (44%)
2 nonadjacent positive levels	6/204 (3%
1 positive level	69/204 (34%)

BMI, body mass index; NSAIDs, nonsteroidal antiinflammatory drugs.
*Scores on the VAS for average recall low back pain over past seven days range from 0 to 10, with higher scores indicating more severe pain.
†Scores on the ODI range from 0 to 100, with higher scores indicating more severe disability.
‡Scores on the EQ-5D-5L index range from −0.5 to 1, with higher scores indicating better quality of life.

long-term use of the therapy. In addition, one participant was withdrawn for resolution of pain without having the device removed. Devices were removed in a further 27 participants for inadequate pain relief, in five participants for postimplant infection, and in one participant to facilitate management of unrelated comorbidities. Because magnetic resonance imaging conditionality of the system had not yet been indicated, ten participants had their system removed before they underwent a magnetic resonance imaging procedure. Fourteen participants were lost to follow-up, and one participant died from unrelated causes. Figures 2 and 3 summarize total participant accountability and detail by follow-up period.

Five-Year Outcomes

Complete Cases (n = 126)

Key efficacy outcomes progressively improved over time, and changes from baseline were clinically substantial and statistically significant at all follow-up visits ($p < 0.0001$; Fig. 4, Table 3). By five years, mean average low back pain had improved from 7.3 ± 0.2 cm at baseline to 2.4 ± 0.2 cm, a change of −67.5% ± 3.1% (95% CI −73.5 to −61.5; $p < 0.0001$); 89 of 124 participants (71.8%) had a reduction in VAS of ≥50%, and 83 of 124 (66.9%) had resolution of chronic low back pain (VAS of ≤2.5 cm), with an average residual VAS of 0.81 cm. The mean ODI improved from 39.1 ± 10.3 points at baseline to 16.5 ± 1.3 points, a change of −22.7 ± 1.4 (95% CI −25.4 to −20.8; $p < 0.0001$), and 77 of 126 participants (61.1%) had an ODI reduction of ≥20 points. The mean EQ-5D-5L index improved by 0.231 ± 0.018 (95% CI 0.195–0.267; $p < 0.0001$). The proportion of participants with a reduction in low back pain VAS of ≥50% and/or ODI of ≥20 points without an increase in either was 97 of 124 (78.2%). The proportion who exceeded these thresholds in both VAS and ODI was 69 of 124 (55.6%). Of the 52 subjects who were on an opioid-containing medication at baseline and had a five-year visit, 69% either discontinued (46%) or decreased (23%) intake. In addition, of the 74 participants who were not on opioids at baseline, 72 (97%) remained off opioids at the five-year visit.

Withdrawals (n = 78)

Study withdrawals for various reasons are summarized in Figures 2 and 3b,c. For the cohort of 27 participants withdrawn for inadequate response, the mean of the last reported changes from baseline was −0.7 ± 0.5 cm for VAS and 1.5 ± 2.9 points for the ODI; for the cohort of 14 participants withdrawn for loss to follow-up, the mean changes were −3.0 ± 0.8 cm and −22.3 ± 5.6 points; for the cohort of ten participants withdrawn for magnetic resonance imaging, the mean changes were −1.7 ± 1.1 cm and −8.4 ± 8.4 points; and for the cohort of 19 participants withdrawn for resolution of pain (of whom one was not explanted), the mean changes in VAS and ODI were −5.3 ± 0.4 cm and −28.0 ± 3.5 points.

Intention-to-Treat Analysis (N = 204)

Comparisons of the completed-cases analyses (n = 126) with the mixed-effects model for repeated measures, which follows the intent-to-treat principle (N = 204), are presented in Figure 4a–f. Although the implicit imputation of missing data in the mixed-effects model for repeated measures attenuated the completed-case results, all reported outcomes maintained their clinical relevance and statistical significance ($p < 0.0001$). The estimates based on the mixed-effects model for repeated measures show that improvements accrued by the one-year follow-up were maintained through the five-year follow-up. Mean low back pain estimates improved from 7.3 ± 0.2 cm at baseline to 3.3 ± 0.2 cm at five years, a change of −54.4% (95% CI −60.0 to −48.8; $p < 0.0001$), and an estimated 57.6% of participants had a reduction in VAS of ≥50%; 52.9% had resolution of chronic low back pain (VAS of ≤2.5 cm) with an average residual VAS of 0.81 cm. Mean ODI score estimates improved from 39.1 ± 10.3 points at baseline to 20.3 ± 1.1 points, a change of −18.7 ± 1.1 points (95% CI −20.8 to −16.5; $p < 0.0001$), and an estimated 50.0% of participants had an ODI reduction of ≥20 points. Mean EQ-5D-5L index estimates improved

Table 2. Outcomes Reported for Completers and All Participants With Stratified Imputation for Missing Data.

Analysis	Baseline	1 y		2 y		3 y		4 y		5 y	
	Mean ± SD	Mean (SE) or % (*n/N*) (95% CI)*		Mean (SE) or % (*n/N*) (95% CI)*		Mean (SE) or % (*n/N*) (95% CI)*		Mean (SE) or % (*n/N*) (95% CI)*		Mean (SE) or % (*n/N*) (95% CI)*	
	N = 204	*n* = 176	*N* = 204	*n* = 156	*N* = 204	*n* = 133	*N* = 204	*n* = 118	*N* = 204	*n* = 126	*N* = 204
LBP VAS (cm)	7.3 ± 0.7	3.0 (0.2)	3.3 (0.2)	2.4 (0.2)	3.1 (0.2)	2.3 (0.2)	3.2 (0.2)	2.2 (0.2)	3.2 (0.2)	2.4 (0.2)	3.3 (0.2)
Change in VAS (cm)		−4.3 (0.2) (−4.7, −3.9)	−3.9 (0.2) (−4.3, −3.6)	−4.8 (0.2) (−5.2, −4.5)	−4.2 (0.2) (−4.6, −3.8)	−4.9 (0.2) (−5.4, −4.5)	−4.1 (0.2) (−4.5, −3.7)	−5.0 (0.2) (−5.5, −4.6)	−4.0 (0.2) (−4.4, −3.6)	−4.9 (0.2) (−5.3, −4.5)	−3.9 (0.2) (−4.3, −3.5)
Change in VAS (%)		−58.9 (2.6) (−64.1, −53.6)	−54.2 (2.7) (−59.6, −48.9)	−66.6 (2.6) (−71.7, −61.6)	−58.0 (2.8) (−63.4, −52.6)	−67.9 (2.9) (−73.6, −62.2)	−56.3 (2.8) (−61.8, −50.7)	−69.5 (3.0) (−75.4, −63.6)	−55.7 (2.9) (−61.4, −50.0)	−67.5 (3.1) (−73.5, −61.5)	−54.4 (2.8) (−60.0, −48.8)
≥30% VAS improvement		73.9 (130/176) (67.4, 80.4)	68.2 (3.4) (61.2, 74.4)	82.6 (128/155) (76.6, 88.6)	72.1 (3.3) (65.2, 78.1)	83.2 (109/131) (76.8, 89.6)	68.5 (3.5) (61.2, 75.0)	84.5 (98/116) (77.9, 91.1)	68.7 (3.7) (61.1, 75.4)	81.5 (101/124) (74.8, 88.4)	66.1 (3.7) (58.6, 72.9)
≥50% VAS improvement		63.6 (112/176) (56.5, 70.7)	58.7 (3.6) (51.6, 65.5)	71.6 (111/155) (64.5, 78.7)	62.3 (3.6) (55.1, 69.0)	77.1 (101/131) (69.9, 84.3)	63.6 (3.7) (56.1, 70.4)	73.3 (85/116) (65.2, 81.3)	58.8 (3.9) (51.1, 66.1)	71.8 (89/124) (64.1, 79.9)	57.6 (3.8) (50.0, 64.8)
≥70% VAS improvement		46.6 (82/176) (39.2, 54.0)	43.2 (3.6) (36.4, 50.3)	61.3 (95/155) (53.6, 69.0)	53.4 (3.7) (46.2, 60.5)	61.8 (81/131) (53.5, 70.2)	51.3 (3.8) (43.9, 58.7)	58.6 (68/116) (49.7, 67.6)	45.9 (3.9) (38.4, 53.6)	62.9 (78/124) (54.4, 71.4)	49.8 (3.8) (42.3, 57.2)
LBP resolution (VAS ≤2.5 cm)		51.7 (91/176) (44.3, 59.1)	48.0 (3.6) (41.0, 55.0)	65.8 (102/155) (58.3, 73.3)	57.3 (3.6) (50.0, 64.2)	67.2 (88/131) (59.1, 75.2)	55.6 (3.8) (48.1, 62.8)	64.7 (75/116) (56.0, 73.4)	50.8 (3.9) (43.2, 58.4)	66.9 (83/124) (58.7, 75.2)	52.9 (3.8) (45.4, 60.3)
ODI	39.1 ± 10.3	19.0 (1.1)	20.6 (1.1)	17.5 (1.2)	20.1 (1.1)	16.6 (1.3)	20.1 (1.1)	15.2 (1.3)	20.1 (1.1)	16.5 (1.3)	20.3 (1.1)
Change in ODI		−19.9 (1.2) (−22.3, −17.6)	−18.4 (1.1) (−20.4, −16.3)	−21.4 (1.3) (−24.0, −18.7)	−18.9 (1.1) (−20.9, −16.8)	−22.5 (1.3) (−25.1, −19.9)	−18.9 (1.1) (−21.1, −16.8)	−23.6 (1.4) (−26.4, −20.8)	−18.9 (1.1) (−21.0, −16.7)	−22.7 (1.4) (−25.4, −20.8)	−18.7 (1.1) (−20.8, −16.5)
Change in ODI (%)		−50.5 (2.9) (−56.3, −44.8)	−46.4 (2.8) (−51.8, −40.9)	−54.3 (3.2) (−60.6, −48.0)	−47.4 (2.8) (−52.9, −41.9)	−58.0 (3.0) (−64.0, −52.1)	−48.4 (2.9) (−54.0, −42.8)	−60.4 (3.2) (−66.7, −54.1)	−47.7 (2.9) (−53.4, −42.0)	−58.0 (3.1) (−64.2, −51.9)	−47.3 (2.9) (−53.0, −41.7)
≥15-point ODI improvement		68.8 (121/176) (61.9, 75.6)	63.5 (3.5) (56.5, 70.0)	67.1 (104/155) (59.7, 74.5)	59.2 (3.6) (52.0, 66.1)	71.2 (94/132) (63.5, 78.9)	59.6 (3.7) (52.2, 66.6)	73.5 (86/117) (65.5, 81.5)	59.6 (3.8) (52.1, 66.8)	73.0 (92/126) (65.3, 80.8)	59.7 (3.7) (52.3, 66.7)
≥20-point ODI improvement		57.4 (101/176) (50.1, 64.7)	53.5 (3.6) (46.4, 60.4)	61.3 (95/155) (53.6, 69.0)	54.4 (3.6) (47.2, 61.4)	62.1 (82/132) (53.8, 70.4)	52.1 (3.7) (44.7, 59.3)	62.4 (73/117) (53.6, 71.2)	50.7 (3.8) (43.2, 58.1)	61.1 (77/126) (52.6, 69.6)	50.0 (3.8) (42.7, 57.4)
Composite of VAS and ODI											
≥50% VAS and/or ≥20-point ODI improvement		73.3 (129/176) (66.8, 79.8)	67.9 (3.4) (60.9, 74.1)	77.3 (119/154) (70.7, 83.9)	67.6 (3.5) (60.5, 74.0)	82.6 (109/132) (76.1, 89.0)	68.6 (3.5) (61.3, 75.0)	79.5 (93/117) (72.2, 86.8)	64.2 (3.7) (56.6, 71.1)	78.2 (97/124) (71.0, 85.5)	63.3 (3.7) (55.8, 70.2)
≥50% VAS and ≥20-point ODI improvement		47.7 (84/176) (40.3, 55.1)	44.0 (3.6) (37.2, 51.1)	56.5 (87/154) (48.7, 64.3)	49.2 (3.7) (42.1, 56.4)	56.5 (74/131) (48.0, 65.0)	46.8 (3.8) (39.5, 54.2)	56.0 (65/116) (47.0, 65.1)	45.2 (3.8) (37.8, 52.8)	55.6 (69/124) (46.9, 64.4)	44.1 (3.8) (36.9, 51.6)
EQ-5D-5L	0.585 ± 0.174	0.780 (0.012)	0.763 (0.012)	0.797 (0.014)	0.769 (0.012)	0.804 (0.014)	0.765 (0.012)	0.822 (0.015)	0.771 (0.013)	0.807 (0.015)	0.768 (0.013)
Change in EQ-5D-5L		0.198 (0.016) (0.167, 0.229)	0.177 (0.011) (0.155, 0.200)	0.217 (0.018) (0.183, 0.252)	0.183 (0.012) (0.160, 0.206)	0.218 (0.017) (0.185, 0.252)	0.179 (0.012) (0.156, 0.203)	0.241 (0.020) (0.201, 0.280)	0.184 (0.012) (0.161, 0.208)	0.231 (0.018) (0.195, 0.267)	0.183 (0.012) (0.159, 0.206)

(Continues)

Table 2. *Continued*

Analysis	Baseline	1 y		2 y		3 y		4 y		5 y	
	Mean ± SD	Mean (SE) or % (*n/N*) (95% CI)*		Mean (SE) or % (*n/N*) (95% CI)*		Mean (SE) or % (*n/N*) (95% CI)*		Mean (SE) or % (*n/N*) (95% CI)*		Mean (SE) or % (*n/N*) (95% CI)*	
	N = 204	*n* = 176	*N* = 204	*n* = 156	*N* = 204	*n* = 133	*N* = 204	*n* = 118	*N* = 204	*n* = 126	*N* = 204
PPR (%)		65.7 (2.4) (60.9, 70.5)	60.7 (2.6) (55.6, 65.8)	71.6 (2.5) (66.8, 76.5)	62.3 (2.6) (57.2, 67.4)	75.3 (2.4) (70.6, 80.1)	62.2 (2.7) (57.0, 67.4)	79.0 (2.3) (74.5, 83.5)	62.9 (2.7) (57.6, 68.2)	78.3 (2.4) (73.6, 83.1)	63.2 (2.7) (57.9, 68.5)
SGIC "Better" or "Much better"		71.6 (126/176) (64.9, 78.3)	66.4 (3.4) (59.4, 72.8)	78.6 (121/154) (72.1, 85.1)	68.8 (3.4) (61.7, 75.1)	80.3 (106/132) (73.5, 87.1)	66.2 (3.6) (58.8, 72.8)	81.0 (94/116) (73.9, 88.2)	64.6 (3.7) (56.9, 71.5)	83.2 (104/125) (76.6, 89.8)	67.5 (3.6) (60.1, 74.1)
TSQ "Definitely satisfied"		78.2 (136/174) (72.0, 84.3)	73.8 (3.2) (66.9, 79.6)	80.0 (124/155) (73.7, 86.3)	71.3 (3.4) (64.3, 77.5)	86.4 (114/132) (80.5, 92.2)	72.2 (3.4) (65.0, 78.5)	91.2 (103/113) (85.9, 96.4)	73.9 (3.5) (66.5, 80.2)	88.0 (110/125) (82.3, 93.7)	72.4 (3.5) (65.1, 78.6)
GCI "Much better"		73.3 (129/176) (66.8, 79.8)	68.7 (3.4) (61.8, 74.9)	78.4 (120/153) (71.9, 84.9)	69.6 (3.4) (62.6, 75.9)	81.4 (105/129) (74.7, 88.1)	68.4 (3.6) (61.0, 74.9)	82.9 (97/117) (76.1, 89.7)	67.3 (3.7) (59.7, 74.0)	83.5 (96/115) (76.7, 90.3)	66.9 (3.7) (59.3, 73.7)

Baseline observation carried forward for participants who withdrew owing to lack of efficacy or explant due to infection. For remaining missing data, continuous outcome estimates from mixed-effects model for repeated measures regression model adjusted for baseline, binary outcomes analyzed with repeated measures logistic models. Statistics are expressed as % (*n/N*) for binary outcomes and *N*, mean (SE) for continuous outcomes.

GCI, global clinical impression; LBP, low back pain; PPR, percent pain relief; SGIC, subject global impression of change; TSQ, treatment satisfaction questionnaire.

*For continuous outcomes, $p < 0.0001$ for two-sided t-test if change from baseline differs from 0.

by 0.183 ± 0.012 (95% CI 0.150 to 0.206; $p < 0.0001$). The estimated proportion of participants with a reduction in low back pain VAS of ≥50% and/or ODI of ≥20 points without an increase in either was 63.3%. The estimated proportion who exceeded these thresholds in both VAS and ODI was 44.1%.

Figure 5 compares the mean relative changes in VAS of the baseline-observation-carried-forward ($n = 32$), missing-at-random ($n = 46$), and five-year completer ($n = 126$) cohorts. The number of five-year completers for whom VAS data were available fluctuated over time owing to missed visits (ie, COVID-19–related) and sporadically incomplete data. The trajectory of the baseline-observation-carried-forward cohort shows mean VAS improvements from baseline, consistent with conservative assumptions. It is noteworthy that the number of participants in the baseline-observation-carried-forward cohort decreases from 32 at baseline to one at four years. Similarly, the trajectory of the missing-at-random cohort approximates the complete case cohort, consistent with the missing-at-random assumptions. The number of participants in the missing-at-random cohort decreases from 46 at baseline to seven at four years. This high-level analysis provides face validity of the assumptions and methods applied.

Safety

Device- or procedure-related serious adverse events (SAEs) are summarized in Table 4, and all occurred within the first year. No additional device- or procedure-related SAEs were reported since. Events through the three-year visit have been discussed previously.[23,25] No lead migrations have been observed throughout the trial. The number and reasons for device removals through the five-year follow-up are presented in Figure 3 and Table 4. It is noteworthy that six participants underwent a surgical revision for lead fracture, and in four of these six cases, the physician elected to replace the implantable pulse generator as a precaution should the battery need replacement in the upcoming years.

DISCUSSION

We report in this study the five-year outcomes of patients who underwent implantation of a restorative neurostimulation system as a part of the ReActiv8-B pivotal trial. Participants had refractory, disabling, mechanical chronic low back pain associated with multifidus muscle dysfunction, and no indication for spine surgery (Table 2). Average pain duration was 14 years, with pain reported on 98% of days in the year before enrollment. Published studies in this condition consistently report that patients with years of refractory, disabling, chronic low back pain very rarely experience spontaneous, substantial, and durable improvements in their pain or disability.[3,4,43] Accrual of substantial and durable improvements was observed in all outcome measures in response to a maximum of two 30-minute sessions of stimulated activation of the dysfunctional multifidus muscles per day. The recovery trajectory is consistent with the hypothesis of a rehabilitative neuromuscular mechanism of action and unlikely to be attributable to an analgesic effect.

At the five-year follow-up, the mean improvements in participant-reported disability, pain intensity, and quality of life were clinically substantial or "very much improved" compared with baseline. Furthermore, improvements in all reported outcomes (Fig. 4a–f, Table 3) were statistically significant ($p < 0.0001$) regardless of the method of analysis.

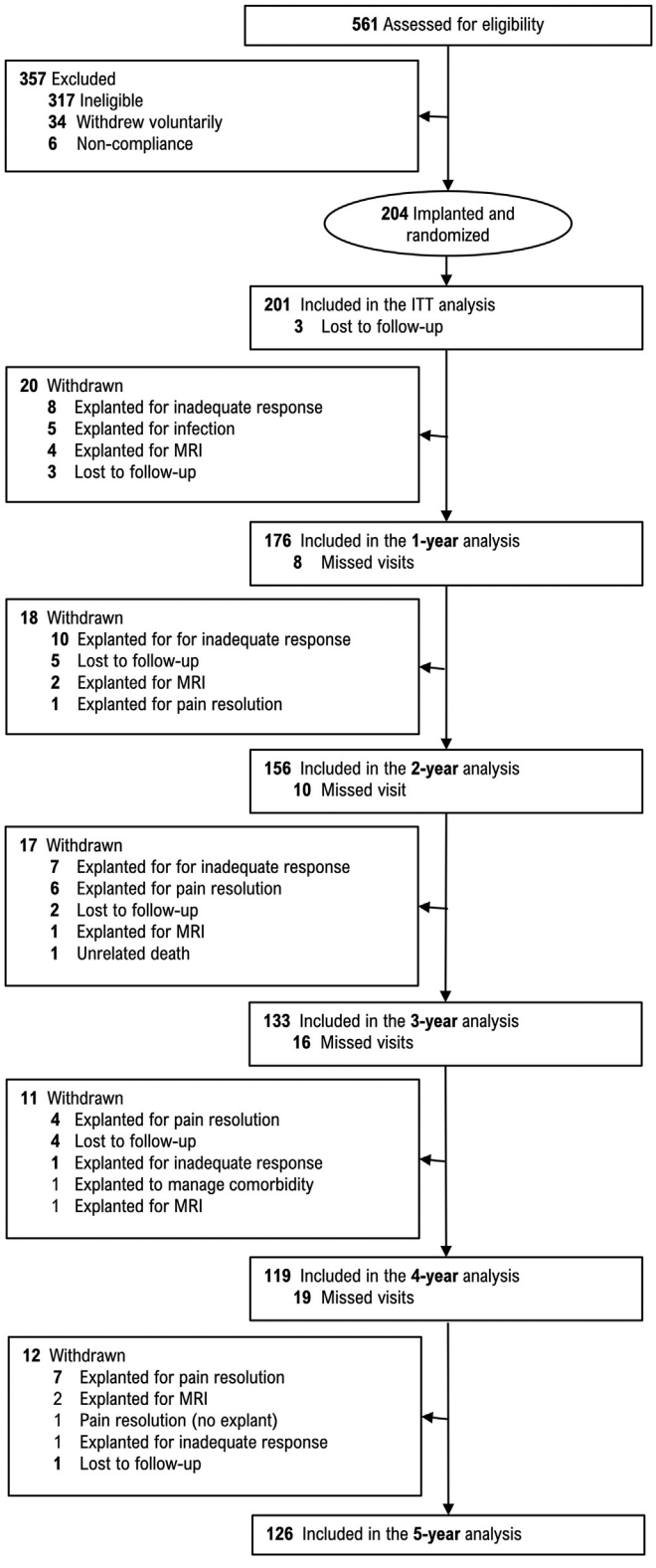

Figure 2. Consolidated Standards of Reporting Trials flow diagram for participant disposition. For conciseness, the parallel randomized phase that was described elsewhere was summarized in one box as "Included in the intent-to-treat analysis" for this prospective, single-arm, open-label continuation of the trial. *One patient voluntarily withdrew after a stroke and elected not to have the device explanted, although they reported resolution of back pain symptoms.

Almost three-quarters of participants in the completer cohort reported a clinically substantial pain reduction (≥50%), and >two-thirds reported resolution of pain (VAS of ≤2.5 cm) and a mean residual VAS of 0.8 cm. Almost three-quarters of participants reported a clinically moderate improvement in low back pain-related disability of ≥15 points on the ODI, and 61% reported a clinically substantial reduction of ≥20 points. From baseline to five years, the ODI improved from 39.1 points, which is at the border between moderate and severe disability, to a mean of 16.5 points, which reflects minimal disability. Lastly, the EQ-5D-5L index for health-related quality of life improved from 0.585 at baseline to 0.807, which closely approached the age-matched United States population norm of 0.815.[44] Of the 52 subjects who were on opioids at baseline and had a five-year visit, almost half had discontinued opioids, and another quarter had decreased intake. In addition, of the 74 participants who were not on opioids at baseline, 72 of 74 (97%) had remained off opioids at the five-year visit.

In patients treated with conventional neurostimulators that rely on palliative analgesic mechanisms of action for pain relief, system explants for resolution of pain are unheard of. For restorative neurostimulation, however, explants for resolution of symptoms increasingly mark the successful conclusion of a rehabilitative treatment trajectory. Through the five-year follow-up, 18 participants underwent elective device removal for resolution of low back pain with a mean residual VAS of 2.3 ± 0.5 cm and ODI of 9.6 ± 2.2 points.

Studies with long follow-up durations, and particularly those for chronic pain conditions, will inherently have to account for missing data because the final outcome may depend on the method chosen.[45] In chronic pain trials, treatment-related withdrawals can be clinical outcomes themselves.[46] An early dropout due to inadequate pain relief usually indicates a treatment failure, whereas a dropout due to resolution of pain signifies treatment success. Imputation using last observation carried forward has been criticized as a source of systematic bias in chronic pain trials.[47] Of the more appropriate, principled methods, the mixed-effects model for repeated measures[48] is the most frequently used imputation approach in chronic pain clinical trials. This method relies on the missing-at-random assumption that future unknown data after subject withdrawal would have likely remained similar if the dropout had not occurred.[45]

The supporting analysis, which follows the intent-to-treat principle ($N = 204$), stratified imputation on the basis of reason for missingness (Table 1). For participants who underwent device explant and withdrawal for infection or inadequate response, baseline observation carried forward was used. For missed visits and device explant and withdrawal for resolution of pain, loss to follow-up, and precautionary explant before magnetic resonance imaging (the missing-at-random cohort), we used the mixed-effects model for repeated measures. Comparison of prewithdrawal data for the baseline-observation-carried-forward and missing-at-random cohorts with all completed cases at every follow-up (Fig. 5) provided a high-level validation of the stratification between baseline observation carried forward and missing at random. The relatively small attenuation between the completed-case and the mixed-effects model for repeated measures, and the statistical significance and clinical relevance of the results in both, instills confidence in the robustness of our data and the validity of the conclusions drawn.

The overall incidence of device- or procedure-related SAEs remained at 8 of 204 (3.9%; Table 4), including the six

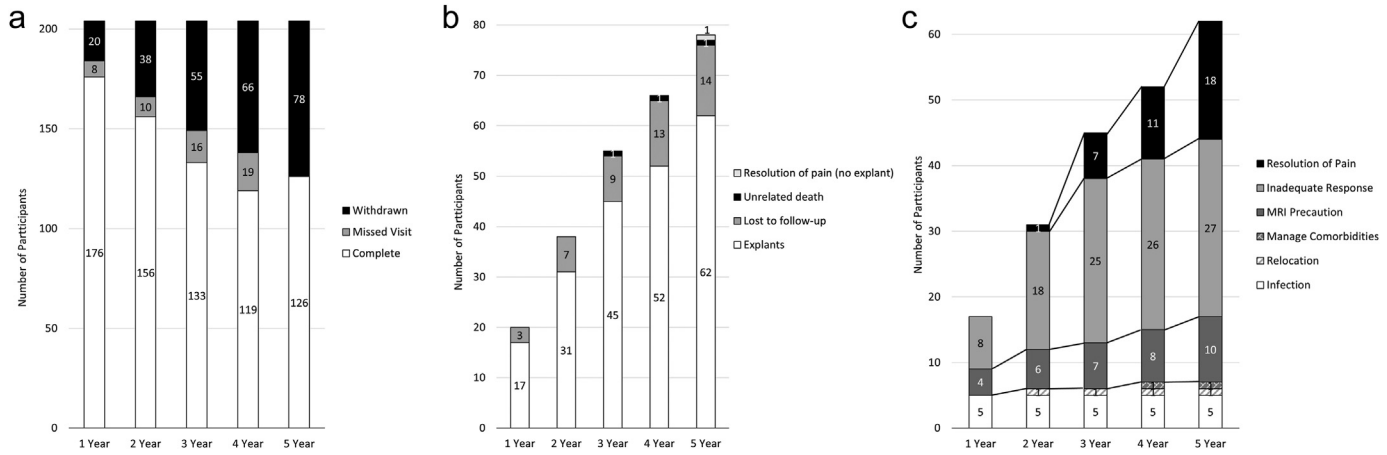

Figure 3. Participant accountability split up by disposition by follow-up (N = 204) (panel a), reasons for withdrawals (panel b), and reasons for permanent device removal (panel c).

postsurgery infections requiring system removal (all reported during the first four months of follow-up). Although no prospective spinal cord stimulator studies provide follow-up beyond three years, the permanent system removal rate for reasons other than resolution of low back pain of 44 of 204 (21.6%) is in line with retrospective spinal cord stimulation literature,[49] and the rate of participants requiring surgical revision of 21 of 204 (10.3%) is comparable to published incidence data for other neuromodulation therapies for chronic pain.[50–52] Lead migration represents the most common device-related adverse event

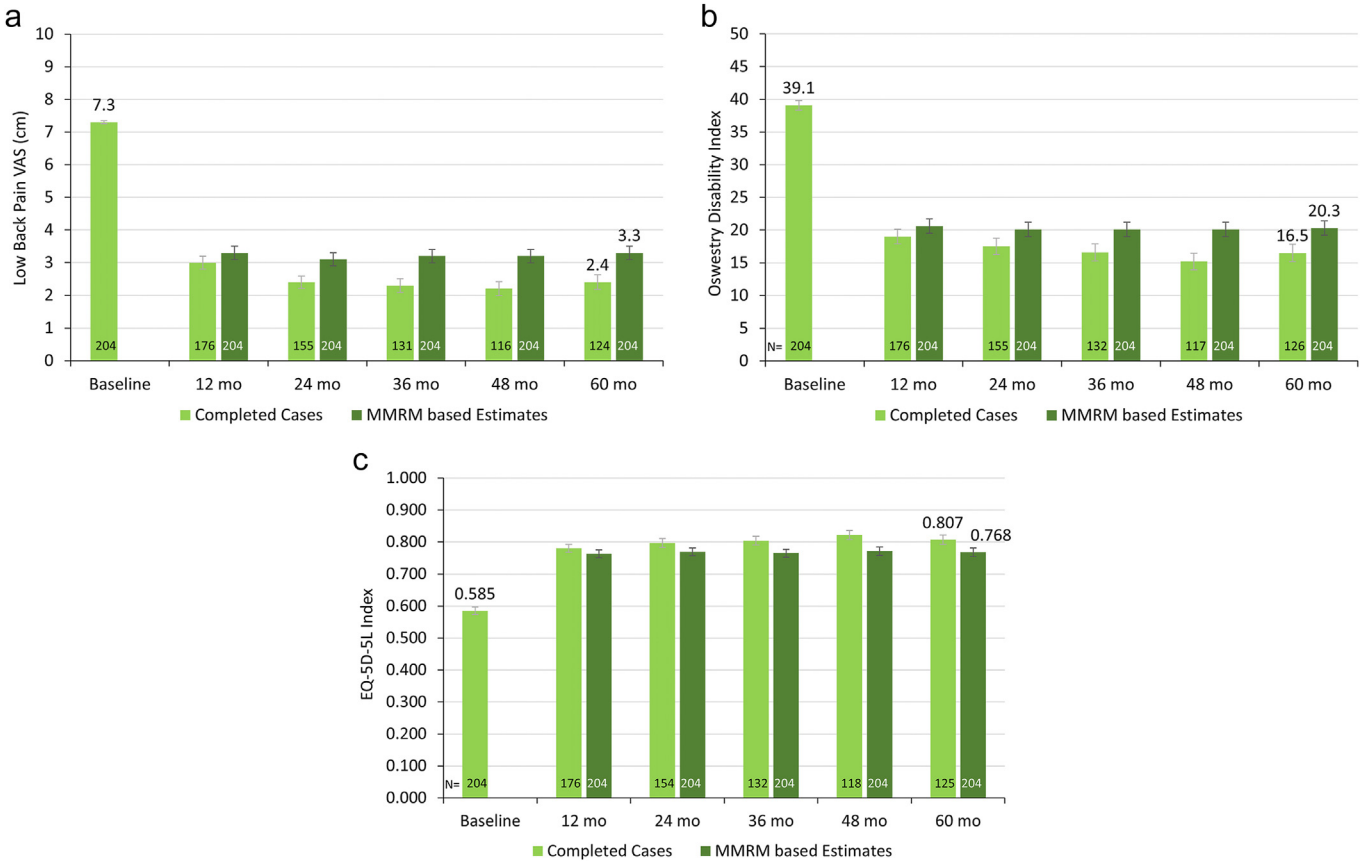

Figure 4. A comparison of the completed-cases analysis for VAS, ODI, and EQ-5D-5L index and the analysis with stratified imputation for missing data following the intention-to-treat principle (N = 204). a–c. The top panels show continuous outcome variables. d–f. The bottom panels show proportion of responders relative to various thresholds. MMRM, mixed model for repeated measures.

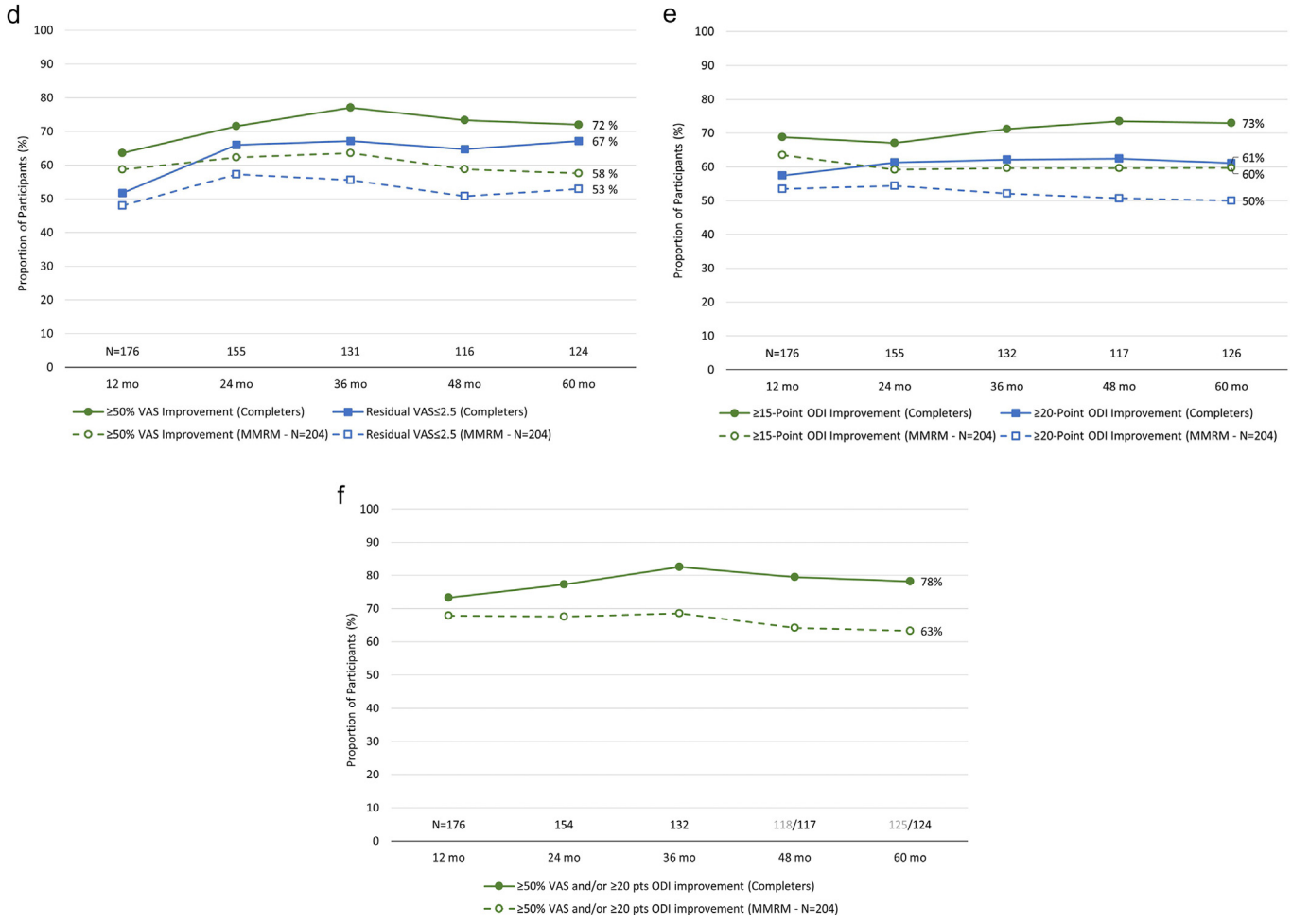

Figure 4. Continued.

reported in neurostimulation trials, occurring at rates of 1.4% to 13.6%.[50,53] Device replacement for battery depletion and lead repositioning are common cost drivers in spinal cord stimulation. It therefore is noteworthy that during the five years of follow-up in this study, no devices were replaced for battery depletion, which indicates the impact of low-dose therapy on battery longevity, and no lead migrations were observed, validating the effectiveness of the distal fixation tines.

The incidence of device removal is expected to decrease in the future because anticipated labeling for magnetic resonance imaging conditionality would have avoided ten removals in this trial. Furthermore, fewer patients may opt for elective removal with smaller next-generation devices. Real-world evidence has shown the positive outcomes in this trial can be duplicated if patients are selected on the basis of the inclusion/exclusion criteria, if the surgical techniques are followed per the instructions for use and mandatory training, and if the patients are educated on recovery occurring steadily over one year and that their treatment compliance is essential.

This prospective, single-arm, open-label continuation of the international, multicenter ReActiv8-B trial has several strengths. The availability of five-year follow-up and outcomes data, which, to the best of our knowledge, is unique for prospective studies with implantable neurostimulators, provides clinically relevant insights into this novel treatment for disabling, mechanical chronic low back pain. Full transparency is provided about participant disposition, missing data, surgical interventions, and procedure- and therapy-related adverse events. To inform interpretation of the completer data, conservative modeling methods following the intent-to-treat principle have been applied to account for missing data.

Potential limitations include that owing to elective cross-over to therapeutic stimulation for ethical and trial-practical considerations, the sham-control group could not be maintained during the long-term follow-ups. This has been elaborated in an earlier publication.[23] Device removals for various reasons, including 18 participants who underwent elective removals for resolution of symptoms (ie, success), contributed to participant withdrawals and subsequent missing data. Although direct correlations with objective device usage and multifidus structure and function were not included in this follow-up, their importance is focus for future work.

CONCLUSIONS

To our knowledge, this is the first prospective study of neurostimulation treatment for chronic low back pain with five-year durability data. Restorative neurostimulation of the lumbar multifidus

Table 3. Device- and Procedure-related SAEs and Surgical Interventions.

Type of event and reason	0–12 mo	12–24 mo	24–36 mo	36–48 mo	48–60 mo
	Patients *n/N* (%)	Patients *n/N* (%)	Patients *n/N* (%)	Patients *n/N* (%)	Patients *n/N* (%)
Device- and procedure-related SAEs					
Infection (resolved)*	6/204 (2.9)	—	—	—	—
Intraprocedural upper airway obstruction (resolved)	1/204 (0.5)	—	—	—	—
Nonradicular patch of numbness on thigh (ongoing)	1/204 (0.5)	—	—	—	—
Surgical interventions and reasons					
Permanent system removal†	17/204 (8.8)	14/204 (6.9)	14/204 (6.9)	7/204 (3.4)	10/204 (4.9)
Inadequate response	8/204 (3.9)	10/204 (4.9)	7/204 (3.4)	1/204 (0.5)	1/204 (0.5)
Infection*	5/204 (2.9)	—	—	—	—
Facilitate magnetic resonance imaging	4/204 (2.0)	2/204 (1.0)	1/204 (0.5)	1/204 (0.4)	2/204 (1.0)
Low back pain resolution	—	1/204 (0.5)	6/204 (2.9)	4/204 (2.0)	7/204 (3.4)
Relocation	—	1/204 (0.5)	—	—	—
Manage comorbidities	—	—	—	1/204 (0.5)	—
Removal and reimplant postinfection*	1/204 (0.5)	—	—	—	—
Revision†	10/204 (4.9)	5/204 (2.5)	2/204 (1.0)	1/204 (0.5)	5/204 (2.5)
Lead replacement	6/204 (2.9)	4/204 (2.0)	2/204 (1.0)	—	2/204 (1.0)
System replacement	—	—	—	1/204 (0.5)	3/204 (1.5)
Pulse generator repositioning‡	4/204 (2.0)	1/204 (0.5)	—	—	—

*One patient was reimplanted after the infection cleared.
†One participant had a system replacement and a permanent system removal during the first year.
‡One participant had a pulse generator repositioning during the first year and a lead revision during the third year.

muscles is a safe, effective, and durable rehabilitative treatment for patients with refractory, disabling, mechanical chronic low back pain associated with multifidus muscle dysfunction. At the five-year follow-up, this patient population that typically has few effective treatment options had accrued durable and clinically substantial benefits in all predefined outcome measures including pain, disability, and health care–related quality of life ($p < 0.0001$ for all), and most participants on opioids eliminated or reduced them. The supporting principled approach for handling missing data instills confidence in the robustness of our data and the validity of the conclusions drawn.

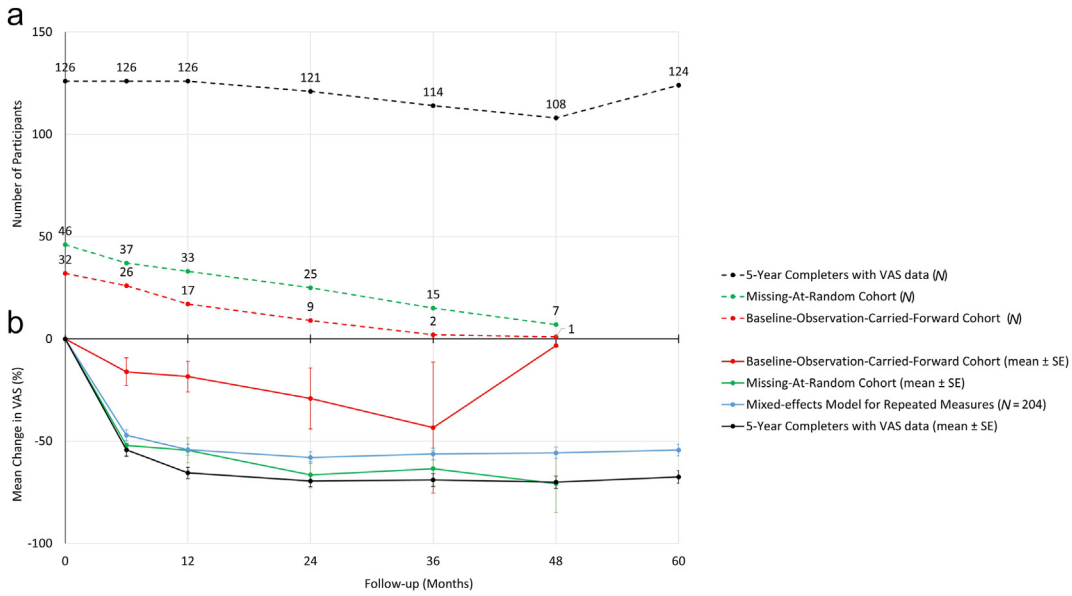

Figure 5. Panel a provides the number of patients with data in the completer cohort (n = 126), the baseline-observation-carried-forward cohort (participants withdrawn for infection and inadequate response), and the missing-at-random cohort (participants withdrawn for reasons assumed at random, including participants explanted for resolution of pain). Panel b compares the relative VAS changes (mean ± SE) of these completer, baseline-observation-carried-forward, and missing-at-random cohorts to provide face validity of the imputation assumptions. The resulting mixed-effects model for repeated measures estimate with implicit imputation for missing data (N = 204) following the intent-to-treat principle is shown in blue.

Table 4. Imputation Stratification by Reason for Missingness.

Reason for missingness	Imputation stratification
Missing data in completer cohort	Inadvertent sporadically missing data points in the completer cohort were considered missing at random.
Missed visits	Isolated missed visits were considered missing at random. Most were due to COVID-19–related scheduling challenges.
Withdrawal for loss to follow-up	Missing data from participants who were declared lost to follow-up after repeated attempts by the site study coordinator to schedule a follow-up were considered missing at random.
Withdrawal for unrelated death	Unrelated death was considered missing at random.
Permanent explants for infection	Although infections hit participants at random, the available outcome data from these patients is considered too limited to treat the missing data as missing at random. Therefore, imputation with baseline observation carried forward (or failure) was used.
Precautionary explants before MRI	In all cases, MRI was performed for comorbidities unrelated to low back pain. Subsequent missing data were considered missing at random.
Explants for inadequate response	Explants requested by the participant because the outcomes did not meet their expectations were considered not missing at random, and baseline observation carried forward (or failure) was used to impute subsequent missing data.
Explants for resolution of symptoms	Although it may seem appropriate to apply last observation carried forward for participants requested removal for resolution of symptoms, subanalysis suggested that mixed-effects model for repeated measures using the missing at random assumption seemed more appropriate.
Explant before remote relocation	Relocation was considered missing at random.
Explant to manage unrelated comorbidities	Management of unrelated comorbidities was considered missing at random

MRI, magnetic resonance imaging.

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Authorship Statements

Christopher Gilligan, Richard Rauck, James Rathmell, Timothy Deer, Shivanand Lad, Jeffrey Fischgrund, Bruce Mitchell, Kristiaan Deckers, Kris De Smedt, Sam Eldabe, Marc Russo, Jean-Pierre Van Buyten, Ganesan Baranidharan, and Vivek Mehta contributed to the development of the protocol. Christopher Gilligan drafted the manuscript. All authors reviewed and approved the manuscript before initial submission. All authors were clinical investigators on the trial, with the following exceptions: Richard Rauck served as chair of the Data Monitoring Committee; James Rathmell served as chair of the Clinical Events Committee; William R. Klemme served as independent magnetic resonance imaging reviewer; Greg Maislin provided statistical support, and Jan Pieter Heemels provided editorial support.

Conflict of Interest

Christopher Gilligan reports stock options received from Mainstay, personal fees from Mainstay, Saluda, Persica, and Iliad Lifesciences, expert witness testimony personal fees, and serving as editor-in-chief of *Pain Practice*; Willem Volschenk reports personal fees from Mainstay; Marc Russo reports personal fees from Mainstay; Matthew Green reports personal fees from Mainstay; Christopher Gilmore reports personal fees and other from SPR, and personal fees from Nevro, Nalu, Biotronik, Boston Scientific, and Saluda; Vivek Mehta reports grants and honoraria from Mainstay and Abbott, personal fees from Boston Scientific, personal fees and honoraria from Medtronic, patent fees from EEPIN-Executive Education Program in Neuromodulation, and leadership/fiduciary role as Chair, Faculty of Pain Medicine UK; Kris De Smedt reports personal fees from Mainstay; Usman Latif reports personal fees from Hydrocision, Spinal Simplicity, Omnia Medical, SPR Therapeutics, and Vertos, and honoraria and personal fees from Nevro and Nalu; Dawood Sayed reports personal fees from Abbott, Boston Scientific, Flowonix, Medtronic, Nevro, Saluda, and Vertiflex, personal fees and stock options from Mainstay, SPR Therapeutics, PainTEQ, and Vertos, and stock options from Neuralace and Surgentec; Peter Georgius reports personal fees from Boston Scientific and Medtronic, lecture support and personal fees from Tilray, lecture support from CSL Seqirus, patent pending personal fees for Arch Bar Wire Application, and personal fees and data safety monitoring/advisory board membership for Presidio; Jonathan Gentile reports personal fees from Mainstay; Bruce Mitchell reports personal fees from Mainstay; Meredith Langhorst reports personal fees from Mainstay and Vivex; Frank Huygen reports grants, personal fees, and honoraria from Abbott and personal fees and honoraria from Saluda; Ganesan Baranidharan reports a grant from Mainstay, grants and personal fees from Nevro, Abbott, Boston Scientific, and personal fees from Nalu and Stryker; Vivek Patel reports personal fees from Mainstay, grants from Orthofix, Pfizer, Premia Spine, Medicrea, Globus, 3-Spine, and Spinal Kinetics, contracts and grants from Aesculap and Medtronic, contracts from Zimmer Biomet Spine, Inc, J&J Medical Device Business Services, NCS America, Simplify Medical, SI Bone, Orthobond Corp, and Cerapedics, consulting fees from Spine Welding, SI Bone, expert testimony for Ogborn Mihm, LLP—Expert Witness Deposition, and support attending meetings from Ecential Robotics and Johnson & Johnson Medical; Alexios Carayannopolous reports consulting fees from

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COMMENTS

This article shows a unique five-year follow-up of a group of patients with mechanical low back pain, receiving therapy with restorative stimulation. There is no better way to show that the treatment is sustainable and considered cost-effective.

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Five-year data in a prospective study are very rare. It's costly, and honorable, and necessary to establish durable safety and efficacy outcomes, especially for completely new methods and treatment paradigms such as medial branch stimulation for multifidus retraining. By now, the interventional spine and neuromodulation community readily accepts this new treatment approach, but payers remain slow to understand the obvious benefit to not only their patients but also their pocketbooks. It remains interesting, and perhaps also a threat to payer acceptance, that more important than the specific underlying radio-pathology is the concept that paraspinal muscle weakness and loss of appropriate recruitment patterns is the primogenitor of likely many underlying painful degenerative spine conditions. This is restorative neuromodulation with robust outcomes and an impressive safety profile. In time, reasonable consideration should be made to place this technology very high in the treatment paradigm; it will likely save spines, lives, and money as secondary, corrective surgeries become quite probably less necessary.

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