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Long-Term Outcomes of Restorative Neurostimulation in Patients With Refractory Chronic Low Back Pain Secondary to Multifidus Dysfunction: Two-Year Results of the ReActiv8-B Pivotal Trial

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ABSTRACT

Background: Impaired neuromuscular control and degeneration of the multifidus muscle have been linked to the development of refractory chronic low back pain (CLBP). An implantable restorative-neurostimulator system can override the underlying multifidus inhibition by eliciting episodic, isolated contractions. The ReActiv8-B randomized, active-sham-controlled trial provided effectiveness and safety evidence for this system, and all participants received therapeutic stimulation from four months onward.

Objective: This study aimed to evaluate the two-year effectiveness of this restorative neurostimulator in patients with disabling CLBP secondary to multifidus muscle dysfunction and no indications for spine surgery.

Materials and Methods: Open-label follow-up of 204 participants implanted with a restorative neurostimulation system (ReActiv8, Mainstay Medical, Dublin, Ireland) was performed. Pain intensity (visual analog scale [VAS]), disability (Oswestry disability index [ODI]), quality-of-life (EQ-5D-5L), and opioid intake were assessed at baseline, six months, one year, and two years after activation.

Results: At two years ($n = 156$), the proportion of participants with ≥50% CLBP relief was 71%, and 65% reported CLBP resolution (VAS ≤ 2.5 cm); 61% had a reduction in ODI of ≥20 points, 76% had improvements of ≥50% in VAS and/or ≥20 points in ODI, and 56% had these substantial improvements in both VAS and ODI. A total of 87% of participants had continued device use during the second year for a median of 43% of the maximum duration, and 60% (34 of 57) had voluntarily discontinued (39%) or reduced (21%) opioid intake.

Conclusions: At two years, 76% of participants experienced substantial, clinically meaningful improvements in pain, disability, or both. These results provide evidence of long-term effectiveness and durability of restorative neurostimulation in patients with disabling CLBP, secondary to multifidus muscle dysfunction.

Clinical Trial Registration: The study is registered on clinicaltrials.gov with identifier NCT02577354.

Keywords: Chronic low back pain, durability, functional segmental stability, multifidus muscle, restorative neurostimulation

Conflicts of Interest: Mainstay Medical ("Mainstay") funded this pivotal regulatory trial and compensated all investigators and committee members either directly (personal fees) or indirectly (payments to institution). Travel expenses related to investigator meetings and training were reimbursed only with prior authorization.

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INTRODUCTION

Most cases of acute low back pain resolve spontaneously without treatment, but for chronic low back pain (CLBP), the prognosis is not favorable.[1] Patients with CLBP often endure impaired quality of life, depression, anxiety, and sleep disturbance.[2,3] Most CLBP patients suffer from mechanical/musculoskeletal pain that is predominantly nociceptive in nature and have no indication for spine surgery.[4–7]

The multifidus muscles are the most important stabilizers of the lumbar spine and play a crucial role in providing segmental stability in response to changes in posture and protection against sudden perturbations.[8–10] Mechanical CLBP is often associated with impaired neuromuscular control and degeneration of the lumbar multifidus muscles.[9,11–13] Persistent back pain–induced inhibition and disruption of proprioceptive signaling have also been linked to long-term motor cortex reorganization.[14] Results of motor control exercise programs specifically targeting the multifidus muscle are mixed.[15,16] The isolated muscle contractions required to reverse impaired neuromuscular control are difficult to achieve voluntarily, especially in the presence of underlying inhibition and degeneration of the multifidus muscle.[17,18] To overcome these limitations to rehabilitation, a restorative neurostimulation system (ReActiv8, Mainstay Medical, Dublin, Ireland) was developed to electrically stimulate the medial branch of the L2 dorsal ramus nerve to elicit isolated multifidus muscle activation.[19,20]

A recent double-blind, randomized, sham-controlled pivotal trial provided safety and effectiveness evidence for premarket approval from the United States Food and Drug Administration (FDA) in 2020.[21]

The objective of the prospective, observational analyses reported here was to evaluate the two-year effectiveness of this restorative neurostimulator in patients with disabling CLBP secondary to multifidus muscle dysfunction and no indications for spine surgery.

MATERIALS AND METHODS

Data for this secondary analysis were obtained from the cohort of 204 patients enrolled at 26 multidisciplinary centers in the United States, Australia, and Europe in the randomized, sham-controlled, double-blind pivotal trial. All patients were receiving therapeutic stimulation from four months onward. Details regarding patient eligibility, study design, implant procedure, and medium-term results through one year have been previously published.[21]

Patients

Study participants were adults with a diagnosis of disabling mechanical CLBP (ie, a seven-day recall of average LBP of ≥6.0 and ≤9.0 cm on the 10-cm visual analog scale [VAS] and Oswestry disability index [ODI] of ≥21 and ≤60 points on a scale from 0 to 100). Mechanical CLBP was defined as low back pain without significant radicular symptoms. Participants had low back pain on at least half of the days in the previous year, were nonresponsive to a minimum of 90 days of nonsurgical medical management including medication and physical therapy, and had a positive prone instability test result (provocative pain test using 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 consequent lumbar segmental instability.[22] Full eligibility criteria are provided in the Supplementary Data.

Trial Design and Oversight

The 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 all participants provided written informed consent. Results are reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[23] The study is registered on clinicaltrials.gov with identifier NCT02577354.

Procedures

All participants received the implanted restorative neurostimulation system (Fig. 1).

During the open-label phase of the trial, all devices were programmed to deliver therapeutic stimulation at a frequency of 20 Hz, a pulse width of 214 μsec, and participant-specific pulse amplitudes and electrode configurations to elicit tonic multifidus contractions for 10 seconds twice per minute. All 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.

Outcomes

Prespecified outcome measures included the seven-day recall of average low back pain on the 10-cm VAS,[24] ODI,[25] EQ-5D index (EuroQol quality-of-life survey [EQ-5D-5L]),[26] percentage of pain relief (PPR), subject global impression of change (SGIC),[27] LBP resolution which we defined as VAS ≤ 2.5 cm, treatment satisfaction questionnaire (TSQ), clinical global impression of change (CGI),[28] and medication usage. These outcomes were assessed and compared with baseline at six months and one and two years, and annual follow-ups are scheduled for a total of five years.

Ongoing safety reporting included serious device- or procedure-related adverse events (AEs) that were actively solicited and documented at each visit and reported and coded according to the Medical Dictionary for Regulatory Activities, version 19.1. The Clinical Events Committee (CEC) adjudicated all AEs.

Data Analysis

Descriptive statistics including mean and standard deviation or standard error of the mean, 95% confidence intervals (CIs), median, first and third quartiles (Q1 and Q3) were used to summarize continuous variables. Binary outcomes were represented as counts and proportions.

To reduce potential bias caused by incomplete follow-up, imputation for missing data was stratified based on the reason for missingness. Baseline observation carried forward, or "failure" for binary outcomes, was used for participants withdrawn for reported lack of efficacy at any time or for permanent explant after infection. For those withdrawn for other reasons (ie, precautionary device removal for magnetic resonance imaging [MRI], resolution of pain, a relocation, or otherwise lost to follow-up) or random missed visits, the mixed-effects model repeated measures (MMRM) approach was used to provide implicit imputations of missing data for continuous outcomes.[29] To evaluate mean changes from baseline, 95% CIs and adjusted paired *t*-tests derived from MMRM

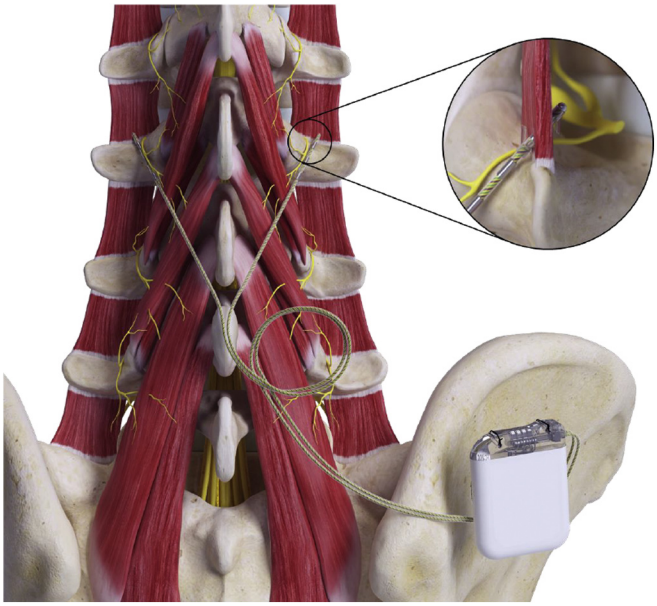

Figure 1. Implantation procedure and materials. Stimulation leads were placed bilaterally near the L2 medial branch of the dorsal ramus nerve as it crosses the L3 transverse process and distally fixated to the L2/3 intertransversarii using flexible tines. The proximal sections were tunneled subcutaneously to the surgically created pocket in the gluteal or lower lumbar region where they were connected directly to the implantable pulse generator. [Color figure can be viewed at www.neuromodulationjournal.org]

contrasts were used. Two-sided p values less than 0.05 were considered statistically significant.

To estimate the proportion of patients achieving "success" for the defined binary outcome variables, multiple imputation (MI) was used for overall estimates of success by visit with associated 95% confidence limits.[30,31]

Analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

Study Population

The demographic and baseline characteristics of the 204 participants are summarized in Table 1. Participants had a mean age of 47 ± 9 years, and 54% were women. The mean duration of CLBP was 14 ± 11 years (range from 7 months to 50 years) from the onset of the first occurrence, and the mean percentage of days with LBP in the previous year was 97 ± 8%. The mean VAS was 7.3 ± 0.7 cm, the mean ODI was 39 ± 10, and the mean EQ-5D-5L index was 0.585 ± 0.174. All participants had undergone physical therapy with an average of 31 ± 52 sessions. Of all participants, 12% had undergone medial branch rhizotomy (>1 year before enrollment), 49% had received spinal injections (>30 days before enrollment), and 37% were taking opioid analgesics for LBP.

Participant Disposition

Longitudinal follow-up data were available for 190 of 204 participants (93%) at six months, 176 of 204 (86%) at one year, and 156 of 204 (79%) at two years (Fig. 2).

At the two-year follow-up, ten participants had missed their follow-up visit, and 38 participants had been withdrawn from the study after permanent system explant (31) or otherwise lost to follow-up (7). One participant in whom the system was explanted for infection was reimplanted after the infection had cleared (Fig. 2).

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

Characteristic	Participants Combined group (N = 204) Mean ± SD or n/N (%)
Age (y)	47 ± 9
Female sex	110/204 (54)
Body mass index (BMI)*	28 ± 4
Pain duration from onset of the first occurrence (y)	14.2 ± 10.6
Percent of days with low back pain in the past year	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)
Number of previous physical therapy sessions	31 ± 52
Medications for low back pain	
At least one medication for low back pain	162/204 (79)
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 (12)
VAS score for low back pain†	7.3 ± 0.7
ODI score‡	39 ± 10
EQ-5D-5L index§	0.585 ± 0.174

*The BMI is the weight in kilograms divided by the square of the height in meters.
†Scores on the VAS for average recall low back pain over the 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 European Quality of Life with five dimensions and five levels (EQ-5D-5L) index range from −0.5 to 1, with higher scores indicating better quality of life.

Two-Year Outcomes

Completed-Cases Analysis (n = 156)

Key efficacy outcomes progressively improved over time, and changes from baseline were statistically significant and clinically meaningful at all follow-ups ($p < 0.0001$; Figs. 3 and 4, Table 2).[32–35] By two years, the mean average LBP VAS had improved by −4.8 ± 0.2 cm (95% CI −5.2 to −4.5; $p < 0.0001$), and 72% of participants had a ≥50% reduction in VAS, with an average reduction of 85%, 62% of participants had a ≥70% VAS reduction, and 67% had resolution of CLBP (VAS ≤ 2.5 cm), with an average residual VAS of 0.97 cm. The mean ODI score decreased by −21.4 ± 1.3 (95% CI −24.0 to −18.7; $p < 0.0001$), and 62% of participants had a ≥20-point ODI reduction, with an average reduction of 32 points. The mean EQ-5D-5L index improved by 0.218 ± 0.017 (95% CI 0.184 to 0.253; $p < 0.0001$). The proportion of participants with a reduction in LBP VAS of ≥50% and/or ODI of ≥20 points without an increase in

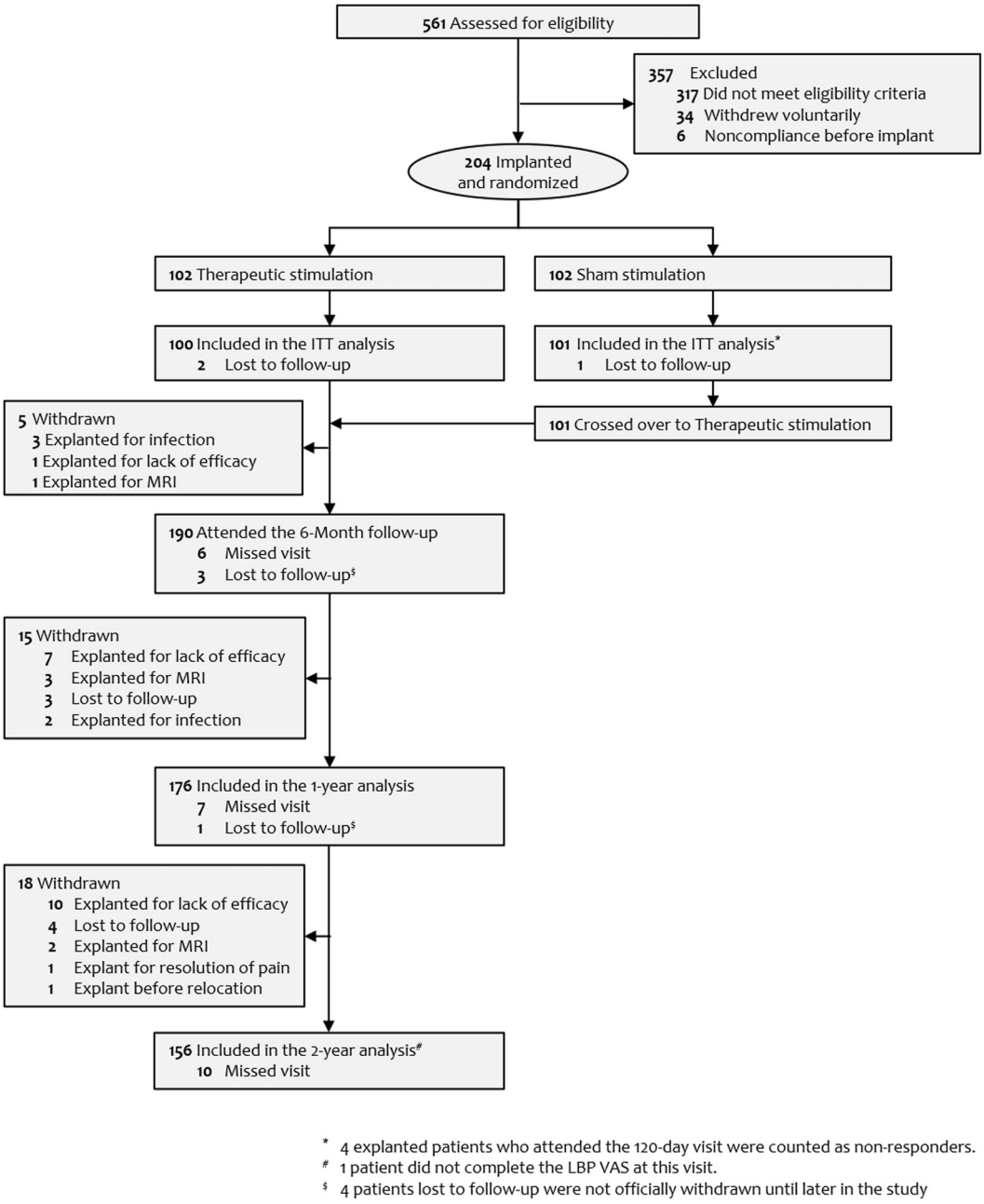

Figure 2. CONSORT flow diagram for participant disposition.

either was 77%. The proportion who exceeded these cut-offs in both VAS and ODI was 57%. Within the cohort of participants with two-year follow-up data, 57 of 156 (37%) were taking opioid analgesics at baseline, 34 of 57 (60%) had voluntarily discontinued (39%) or reduced (21%) opioid use, and 1 of 57 (2%) had increased dosage.

Imputed Analysis ($N = 204$)

A side-by-side comparison of the completed-cases analysis ($n = 156$) and the imputed intention-to-treat (ITT) analysis ($N = 204$) is provided in Table 2. Reported outcomes remained statistically significant ($p < 0.0001$) and clinically meaningful at all follow-ups.

Device Use

Over 94% of participants continued delivering treatment between one and two years. During the 60 days leading to the six-month follow-up, the median device use was 88% (Q1 73%, Q3 96%) of the maximum duration possible (number of days times the maximum duration of 60 minutes daily); for the 90 days leading to the 12-month follow-up, it was 77% (Q1 48%, Q3 90%); and for the 90 days leading to the 24-month follow-up, it was 42% (Q1 6.5%, Q3 75%) (Fig. 5).

Safety Analysis

Device- or procedure-related serious AEs (SAEs) are summarized in Table 3 by follow-up interval. Events through the one-year visit

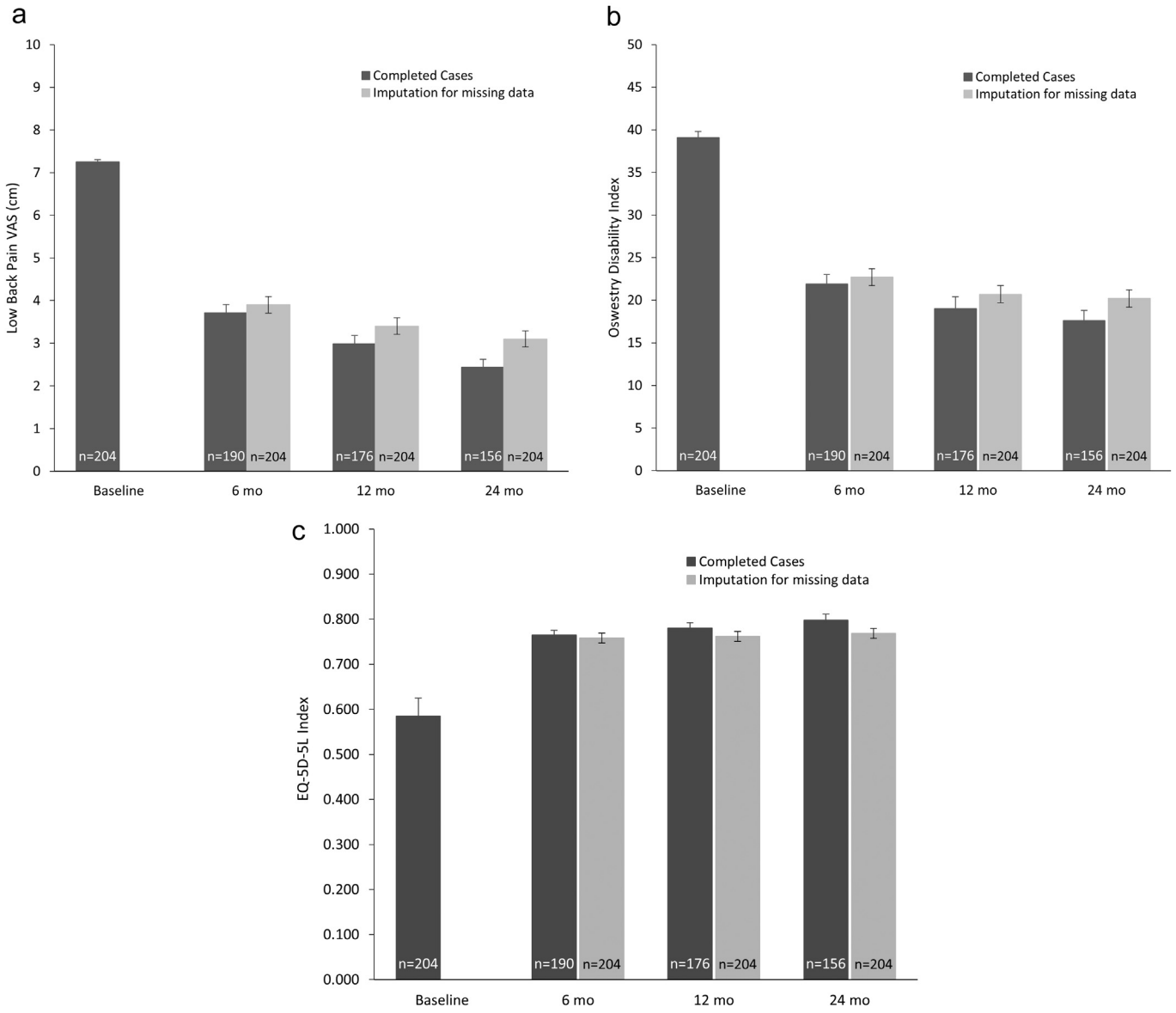

Figure 3. Mean ratings over time for a. low back pain VAS, b. Oswestry disability index, and c. EQ-5D-5L index. All changes from baseline $p < 0.0001$. Error bars represent the standard error of the mean.

have been discussed previously.[21] No additional device- or procedure-related SAEs were reported, and no lead migrations were observed. Overall, 45 of 204 participants (22%) underwent a total of 47 surgical interventions, during which 32 systems were removed (16%), one system was reimplanted (<1%), four pulse generators were repositioned (2%), and ten participants had their leads replaced (5%). Reasons for system removal were lack of efficacy ($n = 18$), infection ($n = 6$), safety precaution before MRI scan ($n = 6$), resolution of LBP ($n = 1$), and relocation to a remote area without device follow-up infrastructure ($n = 1$). Seven unrelated SAEs were reported for seven participants (3%) during the first year, and six unrelated SAEs were reported for six participants (3%) during the second year of the follow-up. All 13 events were reviewed by the CEC and adjudicated as unrelated to the device or procedure.

DISCUSSION

Restorative neurostimulation is indicated for patients with refractory mechanical CLBP secondary to multifidus muscle dysfunction and no pathology seen on MRI that is clearly identified and is likely the cause of the CLBP that is amenable to surgery.

Before enrollment, all participants had failed conventional medical management, which included at least physical therapy and medication for LBP. Most participants had undergone one or more interventional procedures, and over a third were on chronic opioids. Published studies on this condition consistently report that these patients very rarely experience spontaneous, substantial improvements in their pain and disability.[1,36–41]

Longitudinal follow-ups demonstrated a progressive recovery trajectory that is consistent with restoration of multifidus

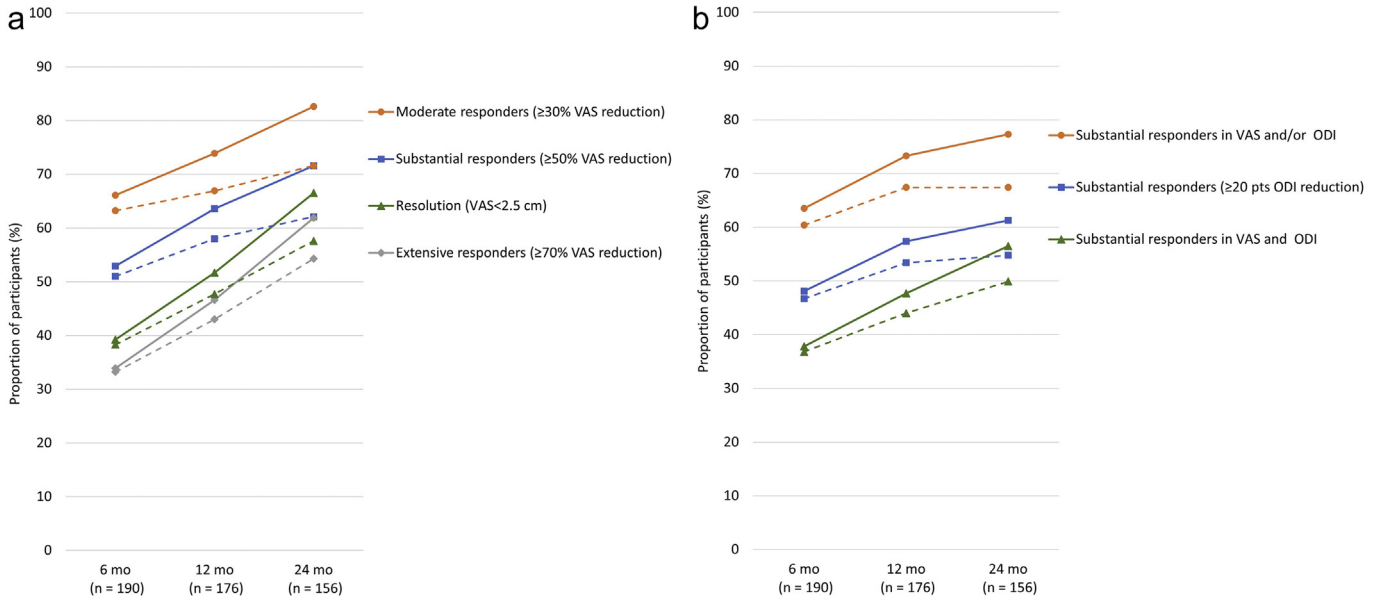

Figure 4. Response rates at common clinical importance thresholds for a. VAS (reduction ≥50% and 70%, and absolute VAS ≤ 2.5 cm), and b. ODI (≥20 points) and composites of VAS and ODI (≥50% and/or 20 points, ≥50% and/or 20 points). Solid lines represent completed cases, and dashed lines represent imputation for missing data (N = 204). [Color figure can be viewed at www.neuromodulationjournal.org]

neuromuscular control. At the two-year follow-up, durable and clinically substantial benefits had accrued in all predefined outcome measures ($p < 0.0001$). Although the study did not directly compare restorative neurostimulation with other available therapies, the improvements were more substantial than those seen with other available therapies for this patient population, such as motor control exercises.[42,43] At baseline, average pain was severe (VAS of 7.3 cm) and disability marginally severe (ODI of 39.1), but after two years of treatment, average pain and disability were mild (2.4 cm and 17.6, respectively). Individual clinical benefits were reflected in the "responder" analysis of the core outcome domains, in which 72% of participants showed a substantial (≥50%) pain reduction,[32] with an average improvement from baseline within this cohort of 84%. A total of 67% of participants reported LBP resolution with an average residual VAS of 0.97 cm, and 61% of participants reported a substantial (≥20 points) ODI improvement,[33] with an average reduction of 32 points from baseline.

Pain and disability are interdependent symptoms of the underlying etiology and codeterminants of a patient's well-being or health state.[44] Improvements in each or both of these outcome domains are recognized as treatment success by patients, physicians, and regulators.[45–47] A total of 77% of participants experienced a substantial improvement in LBP VAS (≥50%) and/or ODI (≥20 points), and 57% experienced such substantial improvements in both. The average EQ-5D-5L utility score had increased from 0.585 to 0.798, which closely approaches the age-matched US population norm of 0.815.[48]

Medication Use

Insufficient relief from existing treatments commonly leads to prescription of chronic opioid therapy for patients with CLBP, despite frequent poor outcomes.[49] Even though participants were considered refractory to pain medication, 76 of 204 (37%) were receiving chronic opioid therapy for their CLBP at baseline. Of the 57 of 156 participants who used opioids at baseline and had a two-year follow-up, 60% had either voluntarily discontinued use or decreased consumption, and only one patient had increased intake. These results suggest that the treatment helps patients voluntarily abandon or reduce opioid consumption. Similar reductions were reported for other LBP medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), simple analgesics, and muscle relaxants, providing further support of clinical benefit.

Device Use

Device use remained high during the second year, with over 94% of participants delivering treatment. Among the 103 of 155 participants (67%) with resolution of CLBP, median device use was 48% (Q1 15%, Q3 74%), which was not materially different from the overall distribution. Eight participants did not administer any treatment during the second year, and four of them had resolution of LBP with a residual average VAS of 1.4 cm. A total of 16 participants had administered over 90% of the maximum permitted treatment amount, and 13 also had resolution of LBP with a residual average VAS of 0.42 cm. This illustrates that even though LBP resolution can be sustained in the absence of stimulation, participants may prefer to continue with therapy delivery despite resolution of their symptoms. Within the remission cohort, three participant profiles are thus emerging: those who stop or minimize stimulation and remain in remission, those who require occasional stimulation to remain in remission or to manage flare-ups, and those who regularly administer a high level of stimulation despite being in remission.

Safety

The overall incidence of related SAEs was 8 of 204 (3.9%; Table 3), including six post-surgery infections requiring system removal, all reported during the first four months of follow-up. The permanent system removal rate of 31 of 204 (15.2%) is in line with spinal cord

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

Analysis	Baseline Mean ± SD	6 mo Mean (SE) or % (n/N) (95% CI)*		1 y Mean (SE) or % (n/N) (95% CI)*		2 y Mean (SE) or % (n/N) (95% CI)*	
	N = 204	*N* = 190	*N* = 204	*N* = 176	*N* = 204	*N* = 156	*N* = 204
LBP VAS (cm)	7.3 ± 0.7	3.7 (0.2)	3.9 (0.2)	3.0 (0.2)	3.4 (0.2)	2.4 (0.2)	3.1 (0.2)
Change in VAS (cm)		−3.6 (0.2)	−3.4 (0.2)	−4.3 (0.2)	−3.9 (0.2)	−4.8 (0.2)	−4.2 (0.2)
		(−3.9, −3.3)	(−3.8, −3.1)	(−4.7, −3.9)	(−4.3, −3.6)	(−5.2, −4.5)	(−4.6, −3.8)
Change in VAS (%)		−48.6 (2.7)	−47.1 (2.6)	−58.9 (2.6)	−54.3 (2.7)	−66.7 (2.6)	−58.1 (2.7)
		(−53.9, −43.3)	(−52.3, −41.9)	(−64.1, −53.6)	(−59.5, −49.0)	(−71.7, −61.6)	(−63.4, −52.8)
≥30% improvement in VAS		66.1 (125/189)	63.2 (3.5)	73.9 (130/176)	66.9 (3.4)	82.6 (128/155)	71.6 (3.3)
		(59.4, 72.9)	(56.5, 70.0)	(67.4, 80.4)	(60.3, 73.6)	(76.6, 88.6)	(65.1, 78.1)
≥50% improvement in VAS		52.9 (100/189)	51.0 (3.6)	63.6 (112/176)	58.0 (3.5)	71.6 (111/155)	62.1 (3.5)
		(45.8, 60.0)	(44.0, 58.0)	(56.5, 70.7)	(51.1, 65.0)	(64.5, 78.7)	(55.1, 69.0)
≥70% improvement in VAS		33.9 (64/189)	33.2 (3.4)	46.6 (82/176)	43.0 (3.6)	61.9 (96/155)	54.3 (3.7)
		(27.1, 40.6)	(26.5, 39.9)	(39.2, 54.0)	(36.1, 50.0)	(54.3, 69.6)	(47.1, 61.5)
LBP resolution (VAS ≤ 2.5 cm)		39.2 (74/189)	38.3 (3.5)	51.7 (91/176)	47.7 (3.5)	66.5 (103/155)	57.6 (3.6)
		(32.2, 46.1)	(31.4, 45.1)	(44.3, 59.1)	(40.7, 54.6)	(59.0, 73.9)	(50.5, 64.7)
ODI	39.1 ± 10.3	21.9 (1.1)	22.7 (1.0)	19.0 (1.4)	20.7 (1.0)	17.6 (1.2)	20.2 (1.0)
Change in ODI		−17.0 (1.1)	−16.4 (1.0)	−19.9 (1.2)	−18.4 (1.0)	−21.4 (1.3)	−18.9 (1.0)
		(−19.2, −14.8)	(−18.4, −14.4)	(−22.3, −17.6)	(−20.4, −16.4)	(−24.0, −18.7)	(−21.0, −16.8)
Change in ODI (%)		−43.0 (2.8)	−41.5 (2.7)	−50.5 (2.9)	−46.4 (2.8)	−54.3 (3.2)	−47.5 (2.8)
		(−48.5, −37.4)	(−46.8, −36.1)	(−56.3, −44.8)	(−51.8, −41.0)	(−60.6, −48.0)	(−53.0, −42.0)
≥20-point improvement in ODI		48.1 (91/189)	46.7 (3.5)	57.4 (101/176)	53.4 (3.5)	61.3 (95/155)	54.8 (3.6)
		(41.0, 55.3)	(39.8, 53.7)	(50.1, 64.7)	(46.5, 60.3)	(53.6, 69.0)	(47.7, 61.9)
Composite of VAS and ODI							
≥50% improvement in VAS and/or ≥20 points ODI		63.5 (120/189)	60.4 (3.5)	73.3 (129/176)	67.4 (3.4)	77.3 (119/154)	67.4 (3.5)
		(56.6, 70.4)	(53.6, 67.2)	(66.8, 79.8)	(60.8, 74.0)	(70.7, 83.9)	(60.4, 74.3)
≥50% improvement in VAS and ≥20 points ODI		37.8 (71/188)	36.8 (3.4)	47.7 (84/176)	44.0 (3.6)	56.5 (87/154)	49.9 (3.6)
		(30.8, 44.7)	(30.0, 43.5)	(40.3, 55.1)	(37.0, 51.1)	(48.7, 64.3)	(42.8, 57.1)
EQ-5D-5L index	0.585 ± 0.174	0.765 (0.010)	0.758 (0.011)	0.780 (0.012)	0.762 (0.011)	0.798 (0.013)	0.768 (0.011)
Change in EQ-5D-5L index		0.180 (0.014)	0.173 (0.011)	0.198 (0.016)	0.177 (0.011)	0.218 (0.017)	0.183 (0.011)
		(0.153, 0.207)	(0.151, 0.194)	(0.167, 0.229)	(0.156, 0.199)	(0.184, 0.253)	(0.161, 0.205)
PPR (%)		55.0 (2.5)	53.3 (2.5)	65.7 (2.4)	60.7 (2.5)	72.1 (2.4)	62.3 (2.5)
		(50.1, 59.9)	(48.4, 58.2)	(60.9, 70.5)	(55.8, 65.6)	(67.3, 77.0)	(57.3, 67.3)
SGIC "Better" or "Much better"		57.4 (109/190)	55.1 (3.5)	71.6 (126/176)	65.9 (3.4)	78.6 (121/154)	68.6 (3.4)
		(50.3, 64.4)	(48.2, 62.0)	(64.9, 78.3)	(59.3, 72.5)	(72.1, 85.1)	(61.9, 75.2)
TSQ "Definitely satisfied"		64.7 (123/190)	62.8 (3.4)	78.2 (136/174)	71.8 (3.2)	80.0 (124/155)	68.3 (3.4)
		(57.9, 71.5)	(56.0, 69.5)	(72.0, 84.3)	(65.5, 78.1)	(73.7, 86.3)	(61.6, 75.1)
CGI "Much better"		56.8 (108/190)	55.0 (3.6)	73.3 (129/176)	67.5 (3.4)	77.6 (118/152)	66.6 (3.6)
		(49.8, 63.9)	(48.0, 62.0)	(66.8, 79.8)	(60.8, 74.1)	(71.7, 84.3)	(59.6, 73.7)

Continuous outcome estimates from mixed model repeated measures regression models adjusted for baseline, all other binary outcomes analyzed with MI for missing data. Statistics are expressed as % (n/N) for binary outcomes and N, mean (standard error) for continuous outcomes.

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

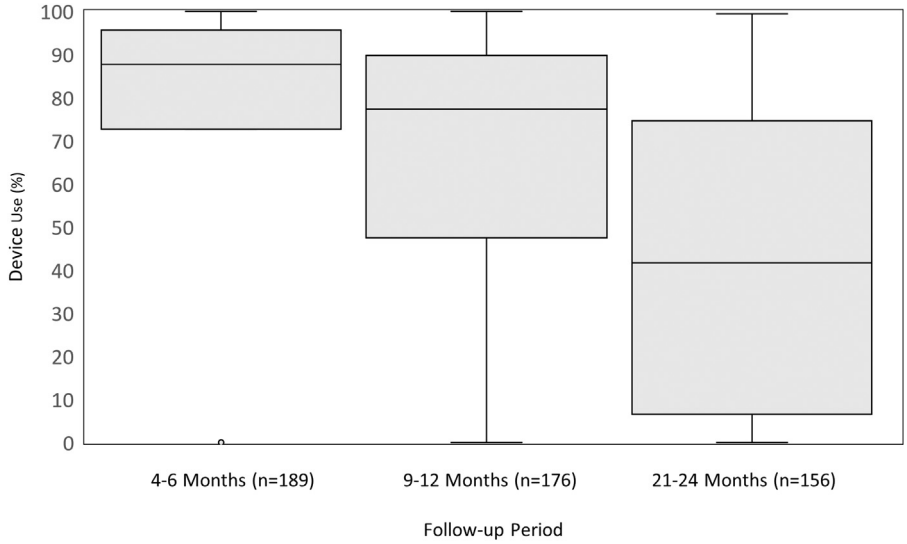

Figure 5. Interquartile ranges of device use as a percentage of the maximum cumulative duration permitted.

stimulation reports over the same two-year period,[50,51] and the rate of participants requiring surgical intervention, 45 of 204 (20%), is comparable with published incidence data for other neuromodulation therapies for chronic pain.[52–54] Lead migration represents the most common AE reported in neurostimulation trials, occurring at the rates of 1.4% to 13.6%.[52,55] No lead migrations were observed in this trial, demonstrating the effectiveness of the distal fixation tines.

Strengths and Limitations

The strength of this study is that it reports on a relatively large and homogeneous cohort of patients with severe and refractory CLBP with an extended follow-up duration of two years. The study demonstrates durable benefits in patients with a baseline pain duration longer than one year. However, because only three patients had a pain duration between 6 and 12 months, the benefits of earlier intervention remain to be studied.

The main limitation is the absence of a long-term comparator because of therapy activation in the sham-control group after conclusion of the blinded phase at four months. Furthermore, studies with long follow-up durations will inherently have to account for missing data, particularly those for chronic pain conditions.[56] Indiscriminate use of last observation carried forward has been criticized as a source of systematic bias in chronic pain trials,[57] and more appropriate methods have been recommended.[58–60] To inform the interpretation of the complete-cases analyses ($n = 156$), we have provided supporting ITT analyses ($N = 204$) using transparent and conservative MMRM imputation, which was stratified based on likely randomness of, and reason for, missing data. The relatively small difference across all outcome measures between

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

Type of event and reason	0–6 mo		6–12 mo		12–24 mo	
	Events *n*	Patients n/N (%)	Events *n*	Patients n/N (%)	Events *n*	Patients n/N (%)
Device- and procedure-related SAEs						
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*						
System removal	8	8/204 (3.9)	11	11/204 (5.4)	13	13/204 (6.4)
Reported lack of efficacy	1	1/204 (0.5)	8	8/204 (3.9)	9	9/204 (4.4)
Infection†	6	6/204 (2.9)	—	—	—	—
Facilitate MRI	1	1/204 (0.5)	3	3/204 (1.5)	2	2/204 (1.0)
Participant relocation	—	—	—	—	1	1/204 (0.5)
LBP pain relief	—	—	—	—	1	1/204 (0.5)
Reimplant post-infection†	1	1/204 (0.5)	—	—	—	—
Revision	5	5/204 (2.5)	5	5/204 (2.5)	5	5/204 (2.5)
Lead replacement	3	3/204 (1.5)	3	3/204 (1.5)	4	4/204 (2.0)
Pulse generator repositioning	2	2/204 (1.0)	2	2/204 (0.9)	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.

the completed-cases and imputed analyses and the statistical significance and clinical relevance of results in both (Table 2) instills confidence in the robustness of our data and the validity of the conclusions drawn.

CONCLUSIONS

The two-year results of the ReActiv8-B trial show durable, statistically significant, and clinically substantial benefits in a cohort of patients with severe, disabling CLBP and multifidus muscle dysfunction who were refractory to conservative care including physical therapy and medications. Participants demonstrated improvements in pain and disability that increased the longer they were treated. This recovery trajectory is consistent with restoration of neuromuscular control and structural muscle changes. The safety profile of the therapy was favorable compared with that of available implantable neurostimulators for the treatment of back pain.

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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, and Sam Eldabe revised 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 Klemme served as independent MRI reviewer, and Jan Pieter Heemels provided editorial support.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2021.10.011.

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COMMENTS

The authors have reported long-term outcome data from the ReActiv8-B pivotal trial. This is an important piece of literature providing evidence of long-term effectiveness and durability of restorative neurostimulation in patients with mechanical chronic low back pain secondary to multifidus muscle dysfunction.

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Multifidus dysfunction plays a pivotal role in chronic low back pain (CLBP). Axial pain is generally difficult to treat with neurostimulation. Furthermore, the rehabilitation that can be carried out with this device opens an important scenario in the treatment of CLBP. The fact that this is not just a symptomatic treatment option is extremely important. The article provides encouraging data regarding quality of life, pain relief, and reduction in opioid intake. I would like to thank the authors for this study that allows us to look forward with confidence in the treatment of patients having CLBP.

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This two-year data of the ReActiv8-B trial shows sustained response and long-term benefit to patients receiving multifidus stimulation therapy long term.

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