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# Three-Year Durability of Restorative Neurostimulation Effectiveness in Patients With Chronic Low Back Pain and Multifidus Muscle Dysfunction

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## ABSTRACT

**Background:** Restorative neurostimulation is a rehabilitative treatment for patients with refractory chronic low back pain (CLBP) associated with dysfunction of the lumbar multifidus muscle resulting in impaired neuromuscular control. The ReActiv8-B randomized, sham-controlled trial provided evidence of the effectiveness and safety of an implanted, restorative neurostimulator. The two-year analysis previously published in this journal demonstrated accrual of clinical benefits and long-term durability.

**Objective:** Evaluation of three-year effectiveness and safety in patients with refractory, disabling CLBP secondary to multifidus muscle dysfunction and no indications for spine surgery.

**Materials and Methods:** Prospective, observational follow-up of the 204 implanted trial participants. Low back pain visual analog scale (VAS), Oswestry Disability Index (ODI), EuroQol quality of life survey, and opioid intake were assessed at baseline, six months, and one, two, and three years after activation. The mixed-effects model repeated measures approach was used to provide implicit imputations of missing data for continuous outcomes and multiple imputation for proportion estimates.

**Results:** Data were collected from 133 participants, and 16 patients missed their three-year follow-up because of coronavirus disease restrictions but remain available for future follow-up. A total of 62% of participants had a ≥ 70% VAS reduction, and 67% reported CLBP resolution (VAS ≤ 2.5cm); 63% had a reduction in ODI of ≥ 20 points; 83% 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 71% (36/51) participants on opioids at baseline had voluntarily discontinued (49%) or reduced (22%) opioid intake. The attenuation of effectiveness in the imputed ($N = 204$) analyses was relatively small and did not affect the statistical significance and clinical relevance of these results. The safety profile remains favorable, and no lead migrations have been observed to date.

**Conclusion:** At three years, 83% of participants experienced clinically substantial improvements in pain, disability, or both. The results confirm the long-term effectiveness, durability, and safety of restorative neurostimulation in patients with disabling CLBP associated with multifidus muscle dysfunction.

**Clinical Trial Registration:** The Clinicaltrials.gov registration number for the study is NCT02577354.

**Keywords:** Chronic low back pain, 3-year durability, Functional segmental stability, Imputation, Neuromuscular control, Multifidus muscle, Opioid reduction, Restorative neurostimulation, Peripheral nerve stimulation

**Conflict of Interest:** Christopher Gilligan reports payment to his institution (for part of his salary) and stock-options received from Mainstay, personal fees from Mainstay, Saluda, Persica, Eli Lilly, Iliad, research funded by Sollis, expert witness testimony 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 from Mainstay and Abbott, grants and personal fees from Boston Scientific and Medtronic; Kris De Smedt reports personal fees from Mainstay; Usman Latif reports personal fees from Hydrocision, Medtronic, Nevro, and Omnia Medical; Dawood Sayed reports personal fees from Mainstay, Abbott, Boston Scientific, Flowonix, Medtronic, Nevro, Saluda, PainTEQ, SPR Therapeutics, Vertos, and Vertiflex; Peter Georgius reports personal fees from Boston Scientific, Abbott and Spectrum; 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 and personal fees from Abbott and Saluda, and nonfinancial support from Boston Scientific; Ganesan Baranidharan reports a grant from Mainstay, grants and personal fees from Nevro, Abbott, Boston Scientific, and personal fees from Nalu and Stryker; Vikas Patel reports personal fees from Mainstay, grants from Orthofix, Pfizer, Premia Spine, Medicrea, Globus, Aesculap, and 3-Spine; Ashish Gulve reports personal fees from Medtronic and Boston Scientific, grants and personal fees from Nevro and Abbott; Jean-Pierre Van Buyten reports personal fees from Mainstay, and grants and personal fees from Medtronic, Nevro, Boston Scientific and Abbott; Antoine Tohmeh reports stock ownership and personal fees with 2 spine companies; Jeffrey Fischgrund reports personal fees from Stryker, Relievant, FzioMed, BioVentus and Asahi Kasei; Timothy Deer reports grants, personal fees, and other from Abbott, Saluda and SPR, grants and personal fees from Boston Scientific, personal fees and other from SpineThera, Nalu, Cornerloc and Ethos, personal fees from Stimgenics, Flowonix and SI Bone, and a patent pending with Abbott; Richard Rauck reports grants from SPR, Nalu and Nevro, personal fees from Presidio, and grants and personal fees from Boston Scientific and Saluda; James Rathmell reports personal fees from the American Board of Anesthesiology, and personal fees from the American Society of Anesthesiology; Frank Schwab reports personal fees from Mainstay, MSD, Zimmer Biomet, Medicrea, Medtronic, and other from VFT Solutions and See Spine; Greg Maislin reports personal fees from Mainstay; Jan Pieter Heemels reports personal fees and equity interests with Mainstay; Sam Eldabe reports personal fees and nonfinancial support from Mainstay, grants and personal fees from Medtronic, and other from Abbott. The remaining authors have no conflict of interest to disclose outside of the submitted work.

For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please see the journal's Guide for Authors.

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## INTRODUCTION

Most cases of acute low back pain (LBP) resolve spontaneously without treatment, but for chronic LBP (CLBP), the prognosis is not favorable.[1] Patients with CLBP often endure impaired quality of life, depression, anxiety, and sleep disturbance.[2,3] Most patients with CLBP suffer from mechanical/musculoskeletal pain 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 anticipated 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] Such contractions cannot be achieved in an effective and painless manner with transcutaneous stimulation devices. 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 double-blinded, 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] Two-year durability and safety data were published in this journal in 2021.[22]

Although all implantable neurostimulation systems aim to provide long-term therapy, few prospective studies have reported follow-up data beyond 1 year. Here we report the 3-year effectiveness and safety data for this restorative neurostimulator in patients with disabling CLBP secondary to multifidus muscle dysfunction and no indications for spine surgery.

The introduction, methods, and study population sections are consistent with those included in the publication of the 2-year results in this journal.[22] For readability, these referenced sections were included with minor adaptations reflecting the longer follow-up duration.

## MATERIALS AND METHODS

Data for this secondary analysis were obtained from the cohort of 204 patients enrolled at 26 multidisciplinary centers in the USA, Australia, and Europe in the randomized, sham-controlled, double-blind pivotal trial. All patients were receiving therapeutic stimulation from four months onwards. Details regarding patient eligibility, study design, implant procedure, and results through two years have been previously published.[21,22]

### 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 LBP without significant radicular symptoms. Participants were not considered surgical candidates for fusion, instrumentation, or decompression (ie, no disruptive or structural spine surgery). In addition, they had LBP on at least half of the days in the year prior to enrolment, were non-responsive to a minimum of 90 days of nonsurgical conservative management, including medication and physical therapy, and had a positive prone instability test (a 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.[23]

### Trial Design and Oversight

Conduct of the trial complied with the FDA regulations, ISO 14155, the 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 following the CONSORT (Consolidated Standards of Reporting Trials) guidelines.[24] The study is registered on clinicaltrials.gov with identifier NCT02577354.

### Procedures

All participants received the implanted restorative neurostimulation system. 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 μs, and participant-specific pulse amplitudes and electrode configurations to elicit strong, 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 side laying using their wireless activator. The device records participant usage and does not permit more than 60 minutes of stimulation in a 24-hour period.

### Outcomes

Prespecified outcome measures included the seven-day recall of average LBP on the 10-cm VAS,[25] ODI,[26] EuroQol quality of life survey (EQ-5D-5L) index,[27] percent of pain relief (PPR), subject global impression of change (SGIC),[28] LBP resolution which we defined as VAS ≤ 2.5 cm, treatment satisfaction question (TSQ) "Are you satisfied with the outcome of your treatment?" (possible answers: "Definitely yes," "Maybe," or "Definitely not"), clinical global impression of change (CGI),[29] and medication usage. These outcomes were assessed and compared with baseline at six months and one, two, and three years. Annual follow-ups are scheduled for additional long-term follow-up.

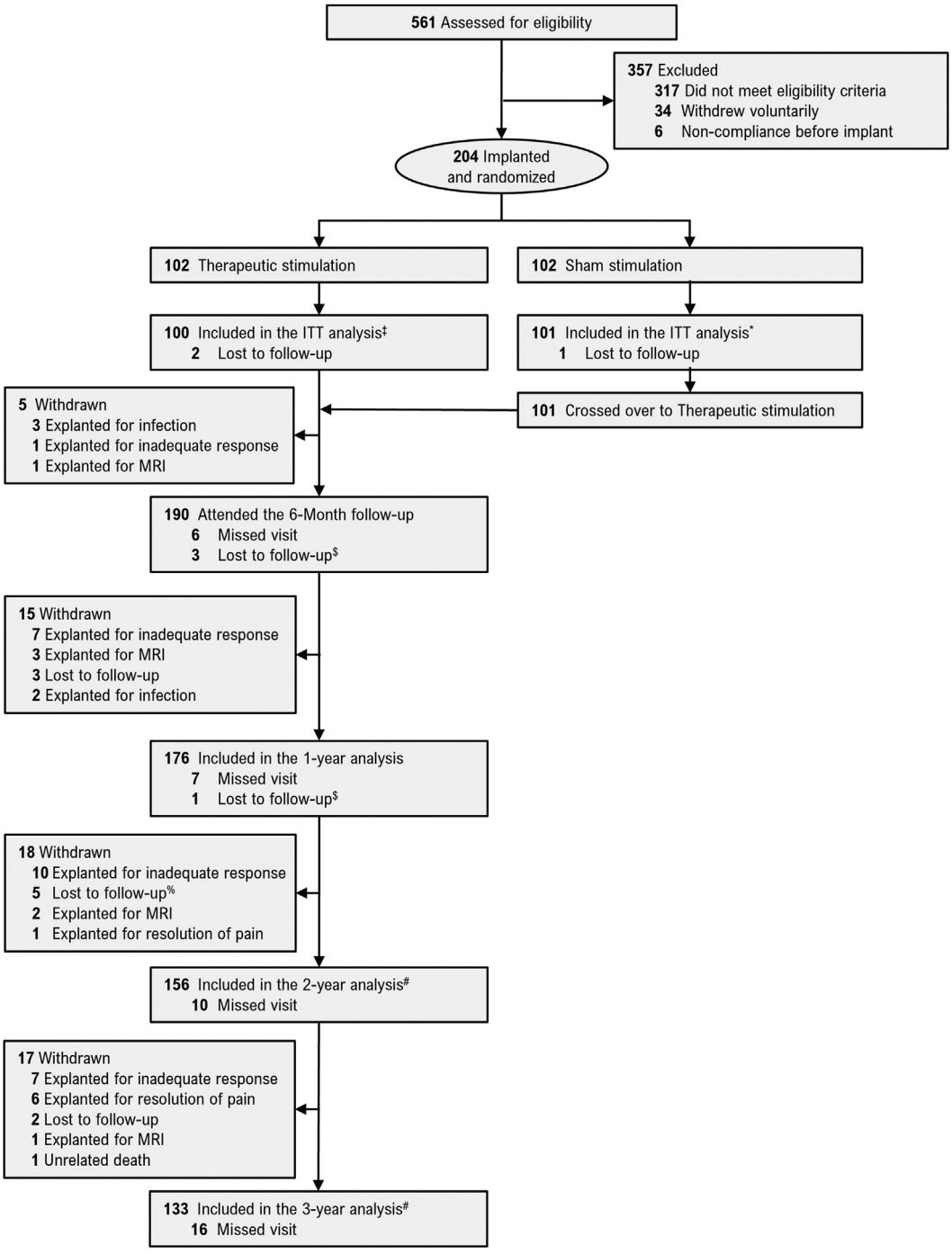
Ongoing safety reporting included serious device- or procedure-related adverse events (AEs), which were actively solicited and documented at each visit and reported and coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1.[30] The Clinical Events Committee (CEC) adjudicated all AEs.

### Data Analysis

Descriptive statistics, including mean and SD or SE of the mean, 95% CIs, and median and interquartile quartile ranges, were used to summarize continuous variables. Binary outcomes were represented as counts and proportions.

To reduce potential bias because of incomplete follow-up, imputation for missing data was stratified based on the reason for missingness. Baseline observation carried forward (BOCF), or 'failure' for binary outcomes, was used for participants withdrawn

for reported inadequate response to therapy at any time or for permanent explant after infection. For those withdrawn for other reasons (ie, precautionary device removal before 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.[31] To evaluate mean changes from baseline, 95% CIs and adjusted paired t-tests derived from MMRM contrasts were used. Two-sided $p$ values $< 0.05$ were considered statistically significant.




‡ 1 participant explanted for infection was reimplanted before primary endpoint assessment.
* 4 explanted participant who attended the 120-day visit were counted as non-responders.
% 1 participant was reclassified from 'Explanted before relocation' to 'Lost to Follow-up' with device implanted.
# 3 participants did not complete the LBP VAS at this visit.
$ 4 participants lost to follow-up were not officially withdrawn until later in the study

**Figure 1.** CONSORT flow diagram for participant disposition.

To estimate the proportion of subjects 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 after applying BOCF for subjects missing because of lack of inadequate response to therapy or device removal because of infection.[32,33]

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

## RESULTS

### Study Population

Demographic and baseline characteristics of the 204 participants were discussed in detail elsewhere.[21] Participants had a mean age of 47 ± 9 years, and 54% were women. The 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 previous year was 97 ± 8%. Mean VAS was 7.3 ± 0.7 cm, mean ODI was 39 ± 10, 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 (> one 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 176/204 (86%) at one year, 156/204 (79%) at two years, and 133/204 (65%) at three years. For 3/133 participants, VAS, ODI, and/or EQ-5D-5L index data were incomplete. This is reflected in the denominator of the reported proportions.

At the three-year follow-up, 149 participants remained active in the trial. However, mainly because of coronavirus disease constraints, three-year visits could not be scheduled for 16 participants. It is expected that most of these participants will yield four-year data.

During the third year of follow-up, 17 participants were withdrawn from the study after permanent system explant (14), being otherwise lost to follow-up (2), or an unrelated patient death (1). Reasons for system removal were inadequate response to therapy ($n = 7$), LBP resolution ($n = 6$), and safety precautions before MRI scan ($n = 1$). Figures 1 and 2 summarize total patient accountability and detail for each follow-up period.

### Three-Year Outcomes

Completed-Cases Analysis ($N = 133$).

Key efficacy outcomes progressively improved over time, and changes from baseline were statistically significant and clinically meaningful at all follow-up visits ($p < 0.0001$; Table 1, Figs. 2 and 3).[34–37] By three years, the mean average LBP had improved by −4.9 ± 0.2 cm (95% CI, −5.3 to −4.5; $p < 0.0001$), and 100/130 (77%) of participants had a ≥ 50% reduction in VAS with an average reduction of 83%; 80/130 (62%) of participants had a ≥ 70% VAS reduction and 87/130 (67%) had resolution of CLBP (VAS ≤ 2.5 cm) with an average residual VAS of 0.92 cm. The mean ODI score improved by −22.7 ± 1.3 (95% CI, −25.3 to −20.1; $p < 0.0001$), and 82/131 (63%) of participants had a ≥ 20-point ODI reduction with an average reduction of 32 points. The mean EQ-5D index improved by 0.220 ± 0.017 (95% CI, 0.186 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 either was 109/131 (83%). The proportion who exceeded these cut-offs in both VAS and ODI was 73/130 (56%). Within the cohort of participants with 3-year follow-up data, 51/133 (38%) were taking opioid analgesics at baseline, and 36/51 (71%) had voluntarily discontinued 25/51 (49%) or reduced 11/51 (22%) opioid dosage.

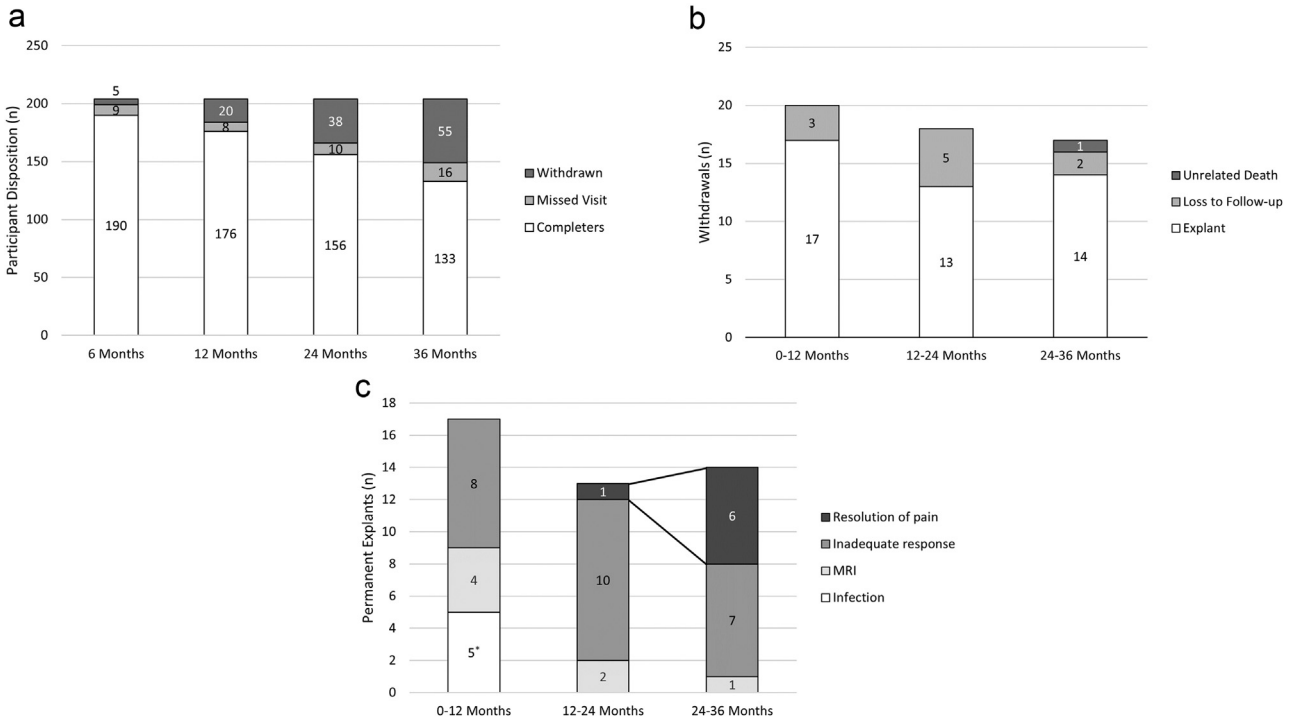



**Figure 2.** Participant accountability split out by (a) disposition by follow-up ($N = 204$), (b) reasons for withdrawals, (c) reasons for permanent device removal. *A sixth participant explanted for infection was reimplanted before the primary endpoint.

**Table 1.** Outcomes Reported for Completers and All Participants With Stratified Imputation for Missing Data.

| Analysis | Baseline | 1 year | | 2 years | | 3 years | |
|---|---|---|---|---|---|---|---|
| | Mean ± SD | 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 |
| LBP VAS (cm) | 7.3 ± 0.7 | 3.0 (0.2) | 3.3 (0.2) | 2.4 (0.2) | 3.1 (0.2) | 2.4 (0.2) | 3.2 (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) (−5.3, −4.5) | −4.0 (0.2) (−4.4, −3.6) |
| Change in VAS (%) | | −58.9 (2.6) (−64.1, −53.6) | −54.2 (2.7) (−59.5, −49.0) | −66.7 (2.6) (−71.7, −61.6) | −58.0 (2.7) (−63.3, −52.7) | −67.4 (2.6) (−73.1, −61.6) | −55.6 (2.8) (−61.1, −50.1) |
| ≥ 30% improvement in VAS | | 73.9 (130/176) (67.4, 80.4) | 74.4 (4.4) (64.7, 82.1) | 82.6 (128/155) (76.6, 88.6) | 79.6 (4.0) (70.7, 86.4) | 82.3 (107/130) (75.7, 88.9) | 73.7 (4.8) (63.2, 82.1) |
| ≥ 50% improvement in VAS | | 63.6 (112/176) (56.5, 70.7) | 63.5 (5.4) (52.4, 73.2) | 71.6 (111/155) (64.5, 78.7) | 68.9 (5.1) (58.0, 78.0) | 76.9 (100/130) (69.7, 84.2) | 69.9 (5.3) (58.7, 79.1) |
| ≥ 70% improvement in VAS | | 46.6 (82/176) (39.2, 54.0) | 41.8 (5.8) (31.0, 53.5) | 61.9 (96/155) (54.3, 69.6) | 58.5 (5.9) (46.7, 69.3) | 61.5 (80/130) (53.2, 69.9) | 54.0 (6.3) (41.8, 65.8) |
| LBP resolution (VAS ≤ 2.5 cm) | | 51.7 (91/176) (44.3, 59.1) | 48.6 (5.9) (37.3, 61.0) | 66.5 (103/155) (59.0, 73.9) | 63.4 (5.6) (51.9, 73.6) | 66.9 (87/130) (58.8, 75.0) | 59.8 (6.0) (47.6, 70.9) |
| ODI | 39.1 ± 10.3 | 19.0 (1.4) | 20.6 (1.0) | 17.6 (1.2) | 20.1 (1.1) | 16.4 (1.3) | 20.1 (1.1) |
| Change in ODI | | −19.9 (1.2) (−22.3, −17.6) | −18.4 (1.0) (−20.4, −16.3) | −21.4 (1.3) (−24.0, −18.7) | −18.9 (1.1) (−21.0, −16.8) | −22.7 (1.3) (−25.3, −20.1) | −18.9 (1.1) (−21.1, −16.8) |
| Change in ODI (%) | | −50.5 (2.9) (−56.3, −44.8) | −46.4 (2.8) (−51.8, −41.0) | −54.3 (3.2) (−60.6, −48.0) | −47.5 (2.8) (−53.0, −42.0) | −58.5 (3.0) (−64.5, −52.6) | −48.4 (2.9) (−54.0, −42.8) |
| ≥ 20 points improvement in ODI | | 57.4 (101/176) (50.1, 64.7) | 58.1 (6.7) (44.8, 70.3) | 61.3 (95/155) (53.6, 69.0) | 59.9 (6.7) (46.3, 72.1) | 62.6 (82/131) (54.3, 70.9) | 54.9 (7.2) (40.8, 68.2) |
| Composite of VAS and ODI | | | | | | | |
| ≥ 50% improvement in VAS and/or ≥ 20 points ODI | | 73.3 (129/176) (66.8, 79.8) | 75.5 (4.5) (60.5, 83.3) | 77.3 (119/154) (70.7, 83.9) | 75.2 (4.7) (64.9, 83.3) | 83.2 (109/131) (76.8, 89.6) | 76.6 (4.7) (66.2, 84.6) |
| ≥ 50% improvement in VAS and ≥ 20 points ODI | | 47.7 (84/176) (40.3, 55.1) | 41.9 (6.5) (29.9, 54.9) | 56.5 (87/154) (48.7, 64.3) | 52.9 (6.8) (39.6, 65.7) | 56.2 (73/130) (47.6, 64.7) | 45.8 (7.0) (32.6, 59.5) |
| EQ-5D-5L index | 0.585 ± 0.174 | 0.780 (0.012) | 0.763 (0.012) | 0.769 (0.012) | 0.768 (0.011) | 0.805 (0.014) | 0.764 (0.012) |
| Change in EQ-5D-5L index | | 0.198 (0.016) (0.167, 0.229) | 0.177 (0.011) (0.155, 0.199) | 0.218 (0.017) (0.184, 0.253) | 0.183 (0.011) (0.160, 0.205) | 0.220 (0.017) (0.186, 0.253) | 0.178 (0.012) (0.156, 0.201) |
| PPR (%) | | 65.7 (2.4) (60.9, 70.5) | 60.7 (2.5) (55.7, 65.7) | 72.1 (2.4) (67.3, 77.0) | 62.3 (2.6) (57.3, 67.3) | 75.3 (2.4) (70.6, 80.1) | 62.2 (2.6) (57.0, 67.3) |
| SGIC "Better" or "Much better" | | 71.6 (126/176) (64.9, 78.3) | 74.6 (4.9) (59.3, 72.5) | 78.6 (121/154) (72.1, 85.1) | 78.8 (4.5) (61.9, 75.2) | 80.0 (104/130) (73.1, 86.9) | 74.2 (5.3) (62.7, 83.1) |
| TSQ "Definitely satisfied" | | 78.2 (136/174) (72.0, 84.3) | 84.1 (3.8) (75.2, 90.3) | 80.0 (124/155) (73.7, 86.3) | 81.1 (4.4) (70.9, 88.3) | 85.5 (112/131) (80.4, 92.2) | 82.3 (4.4) (72.0, 89.4) |
| CGI "Much better" | | 73.3 (129/176) (66.8, 79.8) | 76.6 (4.6) (66.6, 84.4) | 77.6 (118/152) (71.7, 84.3) | 78.2 (4.5) (68.0, 85.8) | 81.4 (105/129) (74.7, 88.1) | 76.1 (5.0) (65.0, 84.4) |

Baseline carried forward for participants who withdrew because of lack of efficacy or explant because of infection. For remaining missing data, continuous outcome estimates from mixed model repeated measures regression models adjusted for baseline; all other binary outcomes analyzed with MI. Statistics are expressed as % (*n/N*) for binary outcomes and *N*, mean (standard error) for continuous outcomes. The imputation model estimates for years 1 and 2 also consider year 3 data and therefore differ slightly from those reported in earlier publications.

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

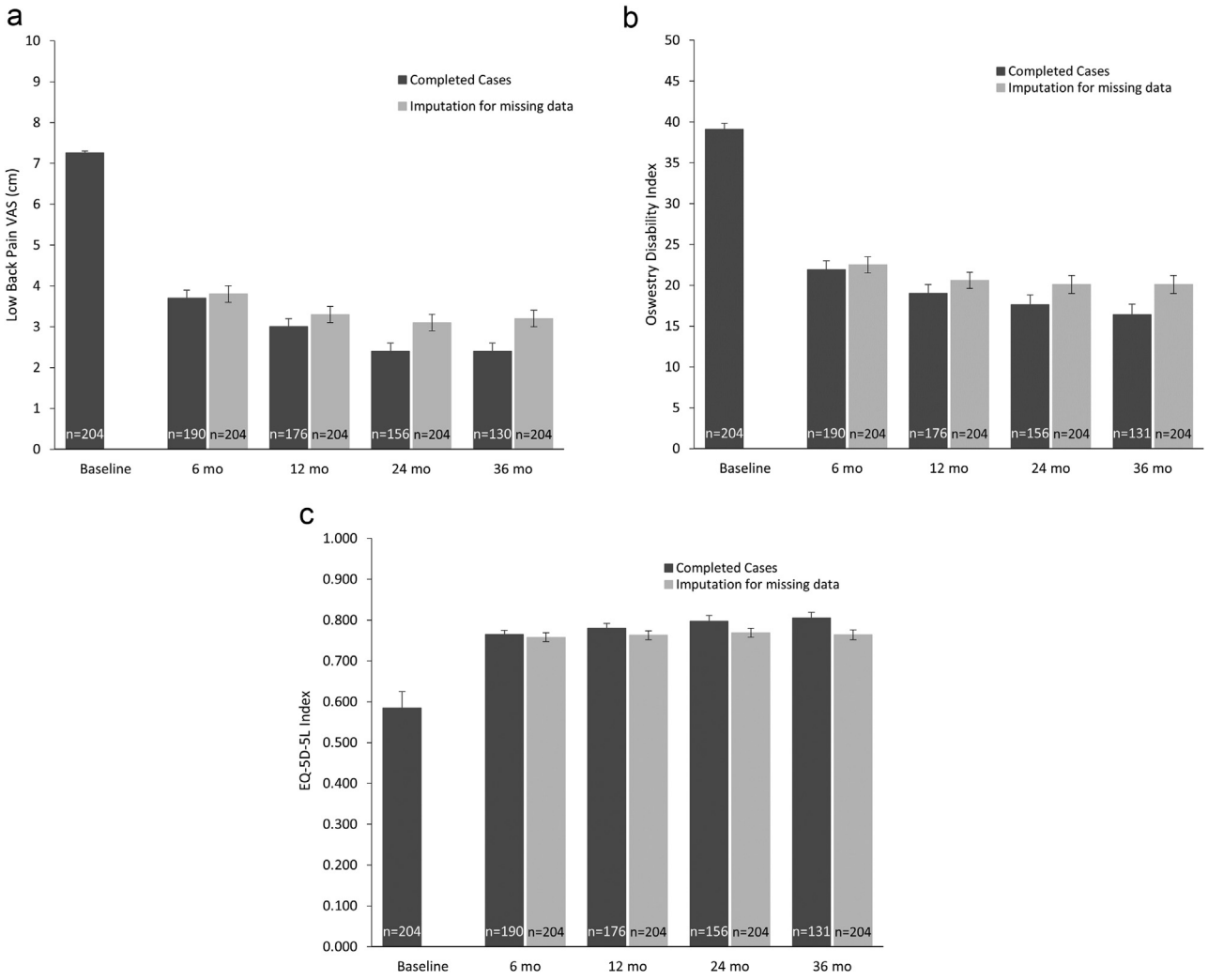



**Figure 3.** Mean ratings over time for (a) low back pain VAS, (b) Oswestry Disability Index, and (c) EQ-5D-5L index. All changes from baseline $p < 0.0001$. Error bars represent the standard error of the mean.

Imputation for Missing Data ($N = 204$)

A side-by-side comparison of the completed-cases analysis ($N = 133$) and the analysis with imputation for missing data ($N = 204$) is provided in Table 1 and Figure 3. Generally, measures of effectiveness were slightly attenuated in analyses that incorporated the strategies for handling missing described previously, but reported outcomes remained statistically significant ($p < 0.0001$) and clinically meaningful at all follow-ups.

### Safety Analysis

Device- or procedure-related serious AEs (SAEs) are listed in Table 2 by follow-up interval. Events through the two-year visit have been discussed previously.[21,22] No additional device- or procedure-related SAEs were reported. No lead migrations have been observed throughout the trial. During the third year of follow-up, 16 participants underwent a surgical intervention, during which 14 systems were removed and leads replaced in 2 participants. Notably, for 6 participants, the reason for device removal was a resolution of back pain. Two unrelated SAEs were reported for 2 (1.5%) participants, with 1 participant suffering multiple traumas after a motorbike accident and another patient who underwent an emergency appendectomy. Both 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 indication for spine surgery.

Before enrollment, all participants had failed conventional medical management, which included at least physical therapy and medication for LBP. Most participants had undergone 1 or more interventional procedures, and over a third were on chronic opioids. Published studies on this condition consistently report that these patients with refractory, disabling CLBP very rarely experience spontaneous, substantial improvements in their pain and disability.[1,38–43]

### Long-Term Treatment Benefits

The three-year results show long-term durability of clinically substantial benefits in pain, function, and healthcare-related quality of life ($p < 0.0001$). The observed progressive improvements over three years are consistent with the putative rehabilitative

**Table 2.** Device- and Procedure-Related SAEs and Surgical Interventions.

| Type of event and reason | 0–12 Months | | 12–24 Months | | 24–36 Months | |
|---|---|---|---|---|---|---|
| | 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) | – | – | – | – |
| Intra-procedural 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 | 19 | 19/204 (9.3) | 12 | 12/204 (5.8) | 14 | 14/204 (6.9) |
| Reported inadequate response to therapy | 9 | 9/204 (4.4) | 9 | 9/204 (4.4) | 7 | 7/204 (3.4) |
| Infection* | 6 | 6/204 (2.9) | – | – | – | – |
| Facilitate MRI | 4 | 4/204 (2.0) | 2 | 2/204 (1.0) | 1 | 1/204 (0.5) |
| LBP Pain Relief | – | – | 1 | 1/204 (0.5) | 6 | 6/204 (2.9) |
| Re-implant post-infection* | 1 | 1/204 (0.5) | – | – | – | – |
| Revision | 10 | 10/204 (4.9) | 5 | 5/204 (2.5) | 2 | 2/204 (1.0) |
| Lead replacement | 6 | 6/204 (2.9) | 4 | 4/204 (2.0) | 2 | 2/204 (1.0) |
| Pulse generator repositioning | 4 | 4/204 (2.0) | 1 | 1/204 (0.5) | – | – |

*One patient was reimplanted after the infection cleared.

mechanism of action in which restoration of multifidus neuromuscular control leads to decreased pain and disability and improved healthcare-related quality of life.[18] The long-term treatment benefits are further illustrated by an increasing proportion of participants who eliminate or decrease opioid consumption. At the three-year follow-up, 49% of participants who were using opioids at baseline had voluntarily discontinued use, compared with 26% and 39% at one and two years, respectively. Similar reductions were reported for other LBP medications, including non-steroidal anti-inflammatory drugs (NSAIDs), simple analgesics, and muscle relaxants.

## Safety

The overall incidence of related SAEs remained at 8/204 (3.9% - Table 2), including the 6 post-surgery infections requiring system removal (all reported during the first four months of follow-up). Although no prospective spinal cord stimulation (SCS) studies provide follow-up beyond two years, the permanent system removal rate for reasons other than the resolution of LBP 38/204 (18.6%) is in line with retrospective SCS reports over the same three-year time period.[44,45] The rate of participants requiring surgical revision 17/204 (8%) is comparable to published incidence data for other neurostimulation therapies for chronic pain.[46–48] Lead migration represents the most common adverse event reported in neurostimulation trials, occurring at rates of 1.4% to 13.6%.[46,49] 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 severely affected patients with refractory CLBP with an extended follow-up duration of three years.

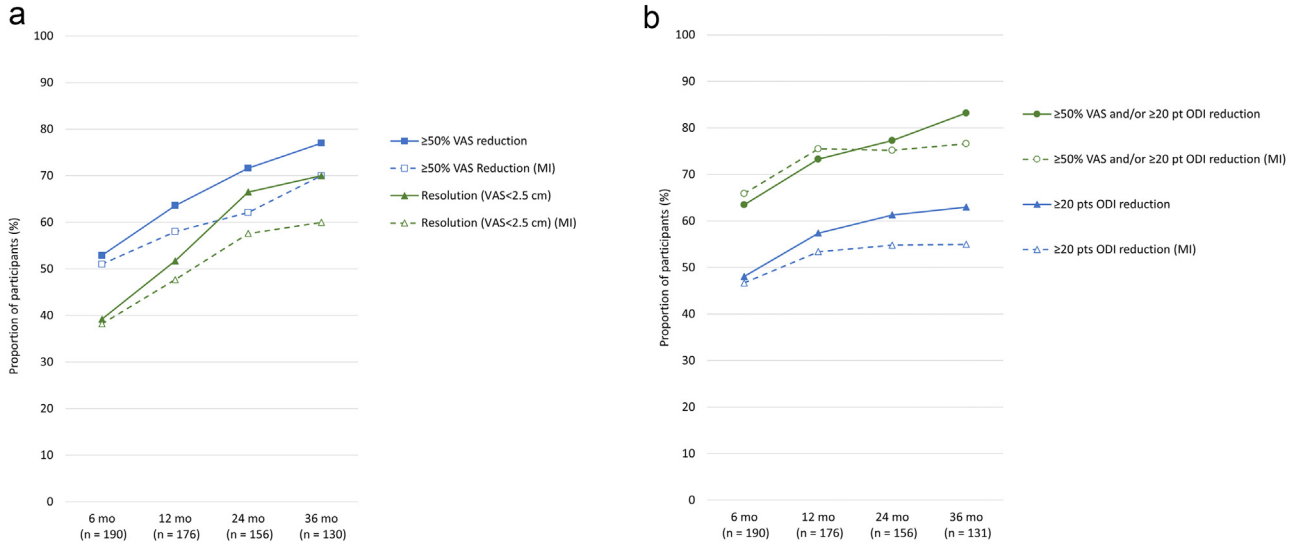



**Figure 4.** Responder proportions at common clinical importance thresholds. a. ≥ 50% VAS reduction and residual VAS ≤ 2.5 cm. b. ≥ 20-point ODI reduction and composite of ≥ 50% VAS reduction and/or ≥ 20-point ODI reduction. Solid lines represent completed cases; dashed lines represent results with MI for missing data (*N* = 204). [Color figure can be viewed at www.neuromodulationjournal.org]

Although all implantable neurostimulation systems aim to provide long-term therapy, only very few prospective studies have reported follow-up data beyond one year, and to our knowledge, no prospective study has reported three-year follow-up results or longer.

Through three years, only 5% (10/204) of patients were withdrawn from the study for loss to follow-up, and for all 45 patients withdrawn from the study after device removal, the reasons were fully documented. These complete, transparent, and accurate accountability records allow for continued accurate effectiveness, durability, and safety updates.

Of 25/204 (12%) participants requesting permanent system removal citing inadequate response to the therapy, 19/25 (76%) had never adequately responded (< 30% VAS improvement), 4/25 (16%) had consistently reported clinically moderate (≥ 30%) or even substantial (≥ 50%) improvements, and 2/25 (8%) participants had a mixed response trajectory. In the context of increasing responder rates over time (Fig. 4), this observation suggests that restorative neurostimulation does not appear to be susceptible to loss of efficacy. Our analysis, however, did not identify risk factors that predispose patients to inadequate response, and this remains an area of ongoing research.

Although SCS system explants for the resolution of pain are very uncommon for restorative neurostimulation, it increasingly marks the successful conclusion of a rehabilitative treatment trajectory. Of the 14 participants who underwent device removal during the third year of follow-up, 6 were for resolution of LBP, compared with 1 during the second follow-up year. Paradoxically, the withdrawal of these participants from the study cohort will negatively impact the complete-case analysis in the same way that device removal and withdrawal for perceived inadequate response to therapy will have a positive impact. Both sources of bias illustrate the importance of providing an analysis with appropriate imputation for missing data alongside the typical complete-case analysis.

Studies with long follow-up durations will inherently have to account for missing data, particularly those for chronic pain conditions.[50] Indiscriminate use of last observation carried forward has been criticized as a source of systematic bias in chronic pain trials,[51] and more appropriate methods have been recommended.[52–54] To inform the interpretation of the complete-case analyses ($N = 133$), we have provided a supporting analysis ($N = 204$) using a principled strategy based on the reason for missingness. Missing data imputation was stratified according to the reason for missingness. Participants explanted and withdrawn for infection or inadequate response to therapy (mean VAS before explant 6.4 ± 2.3 cm) were assigned zero improvement from baseline, and those who were explanted and withdrawn for resolution of pain (mean residual VAS before explant 1.6 ± 1.5 cm) were treated as randomly missing. Participants for whom missingness was not because of infection or inadequate response to therapy were included in the analysis using MMRM for continuous variables or MI for proportions.[31–33] The relatively small attenuation of effectiveness measures across all outcome measures between the completed-case and imputed ($N = 204$) analyses and the statistical significance and clinical relevance of results in both (Table 1, Figs. 3 and 4) instills confidence in the robustness of our data and the validity of the conclusions drawn.

## CONCLUSIONS

The three-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. Consistent with the restoration of neuromuscular control and muscle rehabilitation, participants demonstrated improvements in pain, disability, and healthcare-related quality of life that increased with treatment duration. Approximately half of the patients taking opioids for LBP eliminated them voluntarily. The safety profile of the therapy was favorable compared with available implantable neurostimulators treating other types of back pain, and no lead migrations were observed.

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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, 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 Klemme served as independent MRI reviewer, Frank Schwab contributed data interpretation perspective, and Jan Pieter Heemels provided editorial support.

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## COMMENTS

This is a good piece of work which has shown long term data for the use of Neuromodulation in low back pain.

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This is a very well written long-term follow up paper demonstrating the durability of this therapy in patients with CLBP. The efficacy in patients who continue to get therapy after 3 years seems to be maintained over time. It is also interesting to note that this therapy may be curative in some patients, as a number had their devices removed due to the resolution of their pain.

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