

# New Therapy for Refractory Chronic Mechanical Low Back Pain—Restorative Neurostimulation to Activate the Lumbar Multifidus: One Year Results of a Prospective Multicenter Clinical Trial

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**Objectives:** The purpose of the international multicenter prospective single arm clinical trial was to evaluate restorative neurostimulation eliciting episodic contraction of the lumbar multifidus for treatment of chronic mechanical low back pain (CMLBP) in patients who have failed conventional therapy and are not candidates for surgery or spinal cord stimulation (SCS).

**Materials and Methods:** Fifty-three subjects were implanted with a neurostimulator (ReActiv8, Mainstay Medical Limited, Dublin, Ireland). Leads were positioned bilaterally with electrodes close to the medial branch of the L2 dorsal ramus nerve. The primary outcome measure was low back pain evaluated on a 10-Point Numerical Rating Scale (NRS). Responders were defined as subjects with an improvement of at least the Minimal Clinically Important Difference (MCID) of  $\geq 2$ -point in low back pain NRS without a clinically meaningful increase in LBP medications at 90 days. Secondary outcome measures included Oswestry Disability Index (ODI) and Quality of Life (QoL; EQ-5D).

**Results:** For 53 subjects with an average duration of CLBP of 14 years and average NRS of 7 and for whom no other therapies had provided satisfactory pain relief, the responder rate was 58%. The percentage of subjects at 90 days, six months, and one year with  $\geq$ MCID improvement in single day NRS was 63%, 61%, and 57%, respectively. Percentage of subjects with  $\geq$ MCID improvement in ODI was 52%, 57%, and 60% while those with  $\geq$ MCID improvement in EQ-5D was 88%, 82%, and 81%. There were no unanticipated adverse events (AEs) or serious AEs related to the device, procedure, or therapy. The initial surgical approach led to a risk of lead fracture, which was mitigated by a modification to the surgical approach.

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**Conclusions:** Electrical stimulation to elicit episodic lumbar multifidus contraction is a new treatment option for CMLBP. Results demonstrate clinically important, statistically significant, and lasting improvement in pain, disability, and QoL.

**Keywords:** Arthrogenic muscle inhibition, chronic nonspecific low back pain, electrical stimulation, lumbar multifidus, motor control

**Conflict of Interest:** Dr. Deckers consults for Mainstay Medical, and is a shareholder and advisor for TrainM NV (Antwerp, Belgium). Dr. De Smedt consults for Mainstay Medical and for Medtronic. Dr. Mitchell consults for Mainstay Medical. Dr. Vivian has no conflicts of interest to declare. Dr. Russo consults for Medtronic, Abbott, Boston Scientific, Nevro, Stimwave, Saluda, and Mainstay Medical. He also has equity holdings in Freedom Neuro, Lungpacer, and SPR Therapeutics. Dr. Russo has a patent licensed to Nevro. Dr. Georgius consults for Mainstay Medical, and is a member of the Advisory Boards for Abbott and Boston Scientific. Dr. Green consults for Mundi Phara, Nevro, Abbott, and Boston Scientific. Mr. Vieceli consults for Mainstay Medical. Prof. Eldabe consults for Mainstay Medical, Medtronic, St Jude Medical, Boston Scientific, Saluda Medical, and Axonics. Dr. Gulve consults for Nevro and receives honoraria and travel support from Boston Scientific and Abbott. Member of the European Advisory Board for Boston Scientific. Dr. van Buyten consults for Mainstay Medical, Nevro Corporation, Medtronic, and St. Jude Medical. Dr. Mehta consults for Mainstay Medical. Dr. Ramaswamy has no conflicts of interest to declare. Dr. Baranidharan consults for Mainstay Medical, Abbott, Nevro Corporation, and Boston Scientific. He is a member of the International Advisory Board of Abbott, Nevro, and Boston Scientific. He has an unrestricted research grant from Nevro and Abbott. Dr. Sullivan consults for Nevro, Abbott, Boston Scientific, and Seqiris (Bio CSL). Dr. Gassin consults for Mainstay Medical. Dr. Rathmell consults for Mainstay Medical. Dr. Gilligan consults for Mainstay Medical, Medtronic, Whale Imaging, Axial Healthcare, and Nuvectra.

## INTRODUCTION

Disabling Chronic Low Back Pain (CLBP) impairs quality of life (QoL), impacts healthcare systems and burdens societies worldwide (1–3). For the majority of people suffering from CLBP, it is difficult to identify abnormalities in specific spinal structures as the cause of their symptoms (4,5) and they are often referred to as having Non-Specific Low Back Pain (NSLBP), although some reports advocate the use of precision diagnostic blocks in an attempt to circumvent this (6). NSLBP presents on a spectrum from primarily neuropathic pain (e.g., due to compression of nerve roots in the spinal canal (7)) to primarily nociceptive pain associated with mechanical stress or damage to nonneural tissue (e.g., joints, muscles, ligaments, fascia). NSLBP that is exacerbated by mechanical movements is usually predominantly nociceptive in nature, and is referred to herein as Chronic Mechanical Low Back Pain (CMLBP).

Patients with CMLBP are not typically candidates for spinal surgery, and they seek pain relief utilizing pain management techniques such as noninterventional therapy (e.g., exercise rehabilitation therapy, massage, traction therapy, ultrasound, transcutaneous electrical nerve stimulation [TENS]), pharmacological treatment (e.g., NSAIDs, muscle relaxants, antidepressants, opioids), and/or interventional methods (e.g., nerve blocks, denervation procedures). However, the quality of evidence for the effectiveness of these pain management techniques in this patient population is poor (8–11).

Radiofrequency denervation is also a commonly used technique in the treatment of NSLBP (12), even though it is a treatment aimed at a specific spinal structure, like the facet joints, the sacroiliac joints, or the intervertebral discs. Here too, recent meta-analyses have raised some questions concerning its therapeutic (13) and cost (14) effectiveness, which again might be an illustration of the lack of specificity inherent to NSLBP.

There is no evidence that Spinal Cord Stimulation (SCS) is effective for patients with NSLBP and the European guidelines on NSLBP (15) state that “spinal cord stimulation cannot be recommended for nonspecific CLBP.”

High frequency (10 kHz) SCS has demonstrated superiority compared to conventional SCS in patients with predominantly neuropathic pain (16). However, there is limited evidence of effectiveness in other patient populations. High frequency SCS was evaluated in 20

patients with predominant back pain and no history of spinal surgery (17). However, the authors state this therapy should be “relegated to the subset of chronic back pain patients who present with nonspecific degenerative changes at multiple vertebral levels and complain of severe back pain with clinical characteristics of predominant central sensitization rather than mechanical nociception.”

These conclusions are consistent with the recommendations for the Neuromodulation Appropriateness Consensus Committee (NACC) (18) which found high-level or moderate-level clinical evidence to recommend SCS for neuropathic pain (FBSS, radicular pain, complex regional pain syndrome) but found insufficient, low-quality, or contradictory evidence for SCS use (including high frequency SCS) in patients with predominant low back pain.

Thus, there is a clinical need for treatment options for patients with CMLBP who have failed existing conventional pain management therapies.

While many factors contribute to CMLBP, functional instability at the intersegmental level is one root cause (19,20). The posterior stabilizing muscles, especially the deep fascicles of the lumbar multifidus, play an important role in maintaining intersegmental functional stability (21–24). Following a single episode of debilitating back pain, lumbar multifidus function is often disrupted at the segmental level (25) due to arthrogenic muscle inhibition. Dysfunction of the lumbar multifidus can allow the vertebral segments to move outside their pain-free zone (24), increasing the risk of being reinjured, resulting in potential further motor control impairment, and arthrogenic muscle inhibition, leading to a chronic pain state (26). A detailed review of role of the lumbar multifidus in CMLBP is presented in a companion paper in this issue of *Neuromodulation* (27).

It was hypothesized that motor neurostimulation to elicit episodic contractions of the lumbar multifidus could be used to treat people with CMLBP.

Upon completion of preclinical testing, a feasibility study was conducted in 26 patients to test the hypothesis (28). The results of this feasibility study demonstrated significant and clinically important improvements in low back pain, disability, and QoL at 90-days post activation.

Based on the feasibility study, an implantable neurostimulation device was designed (ReActiv8, Mainstay Medical Limited, Dublin,



**Figure 1.** Photograph of distal end of lead showing four electrodes and opposing tines.

Ireland). This paper reports the results of the first clinical trial to investigate the safety and performance of this device. There was no overlap of subject population in the two studies.

The aim of this trial was to determine if patients with predominant CLBP, with no history of prior surgery, and with unsatisfactory pain relief despite medical management (including at least physical therapy and medication), can obtain clinically meaningful and lasting improvement in their pain by electrical stimulation of the medial branch of the dorsal ramus of the L2 nerve root to elicit episodic contraction of the lumbar multifidus.

## MATERIALS AND METHODS

### Device Description

The device consists of an implanted pulse generator (IPG) and two leads. The proximal end of each lead connects directly to the IPG and the distal end is positioned with four stimulating electrodes in close proximity to the medial branch of the L2 dorsal ramus nerve

as it crosses the L3 transverse processes. The distal end of each lead has tines designed to help fix the lead in the intertransversarius muscles between the transverse processes (Fig. 1) and the lead positioning keeps the distal ends well away from the neural foramen and the dorsal root ganglion (see Fig. 2). The IPG can be programmed to deliver stimulation between any pair of electrodes on each lead.

### Surgical Technique

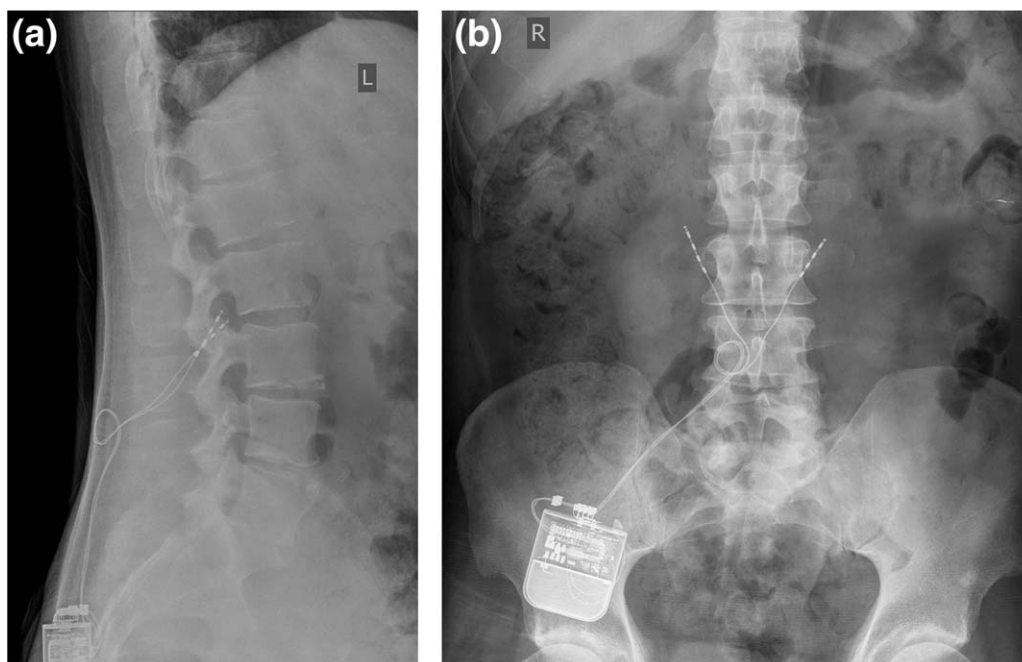
Implant surgery was performed with subjects under general anesthesia or conscious sedation. Leads were placed under fluoroscopy using a modified Seldinger technique with hypodermic delivery needles and a 7F introducer.

In the first 47 subjects, the leads were placed via two incisions under fluoroscopic guidance with the lead body positioned parallel to the spinal column (the “lateral approach”). For the last six subjects and all subsequent lead implants (including lead replacements) the surgical approach was modified so leads were placed from a single midline incision directed laterally to the target (the “midline approach”). The electrodes were placed at the same anatomical target in both the midline and the lateral approaches.

A subcutaneous pocket was created for the IPG using blunt dissection. Leads were tunneled to the IPG pocket and excess lead was looped behind the IPG. The surgical incisions were closed and final A-P and lateral images of the implanted system were obtained.

### Stimulation to Elicit Contraction of the Lumbar Multifidus

The IPG was programmed “Off” at implant, and was reprogrammed to subject appropriate stimulation to elicit strong smooth MF contractions at the Activation visit 14 days after implantation, and reprogrammed if required at each subsequent visit. For all subjects, the stimulation frequency was 20 Hz, the pulse width was 214  $\mu$ sec, and the pulse amplitude and electrode configuration were programmed based on threshold testing on a subject-by-subject basis.



**Figure 2.** a. and b. Lateral-a. and A-P-b. x-Ray images of IPG and leads implanted with the midline approach.

**Table 1.** Key Inclusion and Exclusion Criteria.

## Inclusion criteria

- Age  $\geq 18$  years to  $\leq 65$  years
- Chronic low back pain  $>90$  days to enrolment
- Continuing low back pain despite  $>90$  days medical management within last year

## Exclusion criteria

- BMI  $>35$
- Any current indication for back surgery
- Leg pain worse than back pain or radiculopathy below the knee
- Back Pain Exclusions
  - Any diagnosis or correction of scoliosis
  - Neurological deficit (e.g., foot drop)
  - Sacroiliac joint pain
- Drug Use Exclusions
  - Baseline use  $>120$  mg oral morphine equivalent per day of opioids
  - Current breakthrough dose  $>60$  mg oral morphine equivalent per day

- Medications at stable dose in prior 30 days
- Prior week average NRS of  $\geq 6.0$  and  $\leq 9.0$  at the Baseline Evaluation
- ODI score  $\geq 25\%$  and  $\leq 60\%$  at enrollment

## Surgical Exclusions

- Rhizotomy procedure of medial branch below T8 in prior year
- Anesthetic block of medial branch or epidural steroids for back pain in prior 30 days
- Previous back surgery below T8
- Previous thoracic or lumbar sympathectomy
- Psycho-social exclusions
  - Current/pending litigation, claim or monetary settlement, vlosed claim in past five years, or financial incentive to remain impaired
  - Current active depression

Subjects were instructed to initiate each stimulation session with an Activator while lying prone. The IPG then automatically delivered 10 sec of stimulation followed by 20 sec of no stimulation, which stopped automatically after 30 min. Subjects were asked to perform two 30-min sessions daily—ideally at the same time in the morning and evening. The duration of 60 min per day was chosen based on the results of the Feasibility Study (28) which used 40 min per day and was increased to 60 min following recommendations from investigators. Furthermore, 60 min per day is consistent with physical therapy practice for muscle rehabilitation.

**Trial Design**

ReActiv8-A was an international, multi-center, prospective, single arm trial to characterize the performance and safety of the restorative neurostimulation device to treat patients with refractory CLBP (clinicaltrials.gov NCT01985230). The trial was conducted at ten clinical sites (Australia—5, Belgium—2, and United Kingdom—3) in accordance with ISO 14155:2011. The protocol and associated data collection forms were reviewed and approved by the ethics committee for each site, and informed consent was obtained from each subject prior to enrollment.

Subjects included were adults with chronic ( $>90$  days) predominant low back pain who have not achieved satisfactory relief of their symptoms despite treatment with at least physical therapy and medication; have not had nor are currently indicated for spinal surgery; and are not eligible for SCS (Table 1). Medial branch rhizotomy in the prior year was an exclusion criterion. All subjects had an MRI to exclude anatomical or pathological changes consistent with symptoms that could be amenable to surgery, but presence of multifidus atrophy or fat infiltration on MRI was not an inclusion criterion.

The implant procedure typically took less than one hour, and “on table” testing verified appropriate electrode placement by the ability to achieve isolated contraction of the lumbar multifidus muscle. Follow-up evaluations were scheduled for 45, 90, 180, 270, and 365 days from the day the system was activated. Subjects were asked to not change their pain medications or physical activities until after the 90-day outcome visit. A Data Monitoring Committee (DMC) and a Clinical Events Committee (CEC), each comprised of independent

physicians, provided safety oversight and monitored the trial integrity.

**Outcome Measures**

## Baseline Data

For each subject, a medical history (including back pain history and treatments attempted), work status, and medication usage was documented.

## Performance and Safety Endpoints

The primary performance measure was improvement in low back pain utilizing a 10-point Numerical Rating Scale (NRS) with 0 meaning “no pain” and 10 meaning “worst imaginable pain.” Subjects recorded their daily average NRS in a journal, and the mean NRS was calculated from data recorded in the journal for the prior seven days. The primary efficacy endpoint was a responder analysis where a “responder” was defined as a subject with  $\geq 2$ -point reduction in the mean NRS pain score (29) from baseline to 90 days postactivation without a clinically meaningful increase in consumption of back pain medications as determined and adjudicated by the CEC. For back pain assessments after 90 days, subjects were asked to report their low back pain NRS on the day of the evaluation (single day NRS). A single day NRS was also recorded at the enrollment evaluation.

Secondary performance measures were improvements in disability and QoL. Disability was measured with the 100-point Oswestry Disability Index (ODI) with scores of 21–40% indicating moderate disability and scores of 41–60% indicating severe disability (30). QoL was measured with the European Quality of Life Score on Five Dimensions (EQ-5D, EuroQol Group; <https://euroqol.org/>). The minimal clinically important difference (MCID) for ODI is a change of 10 points (29) and the MCID for EQ-5D is a change of at least 0.03 points (31).

Safety was evaluated by assessing adverse events (AEs) categorized in accordance with the strict definitions of ISO 14155:2011 into nonserious or serious, and further by relatedness to the procedure, device, and/or stimulation. All AEs were adjudicated by the CEC and reported to the regulatory authorities in accordance with local

**Table 2.** Baseline Demographics.

Characteristic (n = 53)	Mean ± SD or N (%)
Age	44 ± 10
Gender (male–female)	23 (43%)–30 (57%)
Duration of back pain (years)	14.3 ± 10.5
Average back pain NRS	6.8 ± 0.8
Disability on Oswestry Disability Index (ODI)	44.9 ± 10.1
Quality of life on EQ-5D	0.434 ± 0.185
Back pain medications	
Opioids	38 (72%)
Analgesics (simple and other)	31 (59%)
NSAIDs	20 (38%)

requirements. In addition, the DMC performed scheduled periodic reviews of the results and AEs to evaluate overall safety.

### Exploratory Endpoints

Several exploratory measures were collected, including the Treatment Satisfaction Questionnaire (TSQ), which measured subject satisfaction with a yes/no question. Subjects who answered “yes” were asked if they are “satisfied” or “very satisfied.”

### Statistical Analysis

A responder analysis was conducted for the primary performance measure (low back pain NRS). Continuous variables were summarized with the number, mean, standard deviation or error, and minimum/maximum values. Categorical variables were presented with the number and proportion of subjects in each category. Binary outcomes were evaluated as proportions. The continuous primary and secondary performance outcomes were assessed for significant change from baseline utilizing a two-sided *t*-test with a *p* value ≤ 0.05 indicating statistical significance. All statistical analyses were conducted utilizing SAS version 9.3, or later (SAS Institute Inc., Cary, NC, USA) or R version 2.14 or later (R Development Core Team, 2012; <https://www.r-project.org/>).

## RESULTS

### Demographics

Key baseline subject demographic data are summarized in Table 2. Of the 53 subjects implanted, data are available on 52 subjects at the 90-day evaluation, 51 subjects at the six-month evaluation, and 47 subjects at the one-year evaluation. By the one-year evaluation a total of five subjects (9.4%) had the system explanted without complications and were withdrawn from the trial. One subject had the system explanted prior to completion of the 90-day evaluation due to lead migration and the remaining four subjects were explanted due to lack of efficacy (nonresponders). Data were missing on one subject at each of the six-month and one-year evaluations. No responder requested explant of the system.

### Operative and Postoperative Details

Subjects were assigned to the Procedure Refinement Cohort (PRC) or the Pivotal Cohort. The PRC allowed 1–3 roll-in subjects at each site to account for any operative learning curve. A total of 13 subjects were included in the PRC across all sites. There were no significant differences in the primary and secondary outcome measures between the PRC and Pivotal groups. However, the surgical procedure time (Mean ± SD), defined as the time from first incision to final suture for closure, decreased from 118 ± 40 min in the PRC group to 75 ± 28 min for the pivotal cohort.

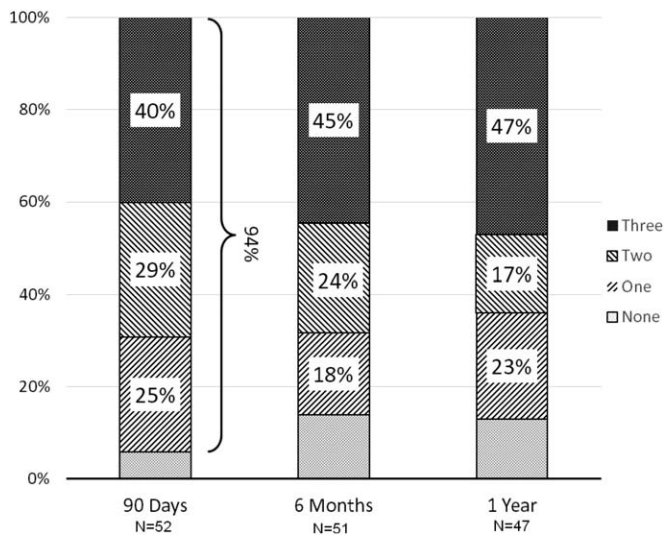
### NRS, ODI, and EQ-5D

The responder rate at 90 days was 58%. Similarly, at one year 57% of subjects had ≥2 point reduction in the single day NRS, 60% had ≥10 point improvement in ODI, and 81% had ≥0.03 point improvement in EQ-5D compared to baseline values. Table 3 summarizes the primary and secondary performance outcomes to the one-year evaluation.

People tend to adjust their lifestyle according to personal trade-offs—some might favor an improvement in pain over increased activity, while others might prefer improvements in activity and reduction in drugs with the same level of pain as before. A posthoc analysis was performed to evaluate composite success based on satisfying the MCID of at least one of the key outcome measures (NRS, ODI, or EQ-5D). As illustrated in Figure 3, at 90 days, six months, and

**Table 3.** Primary and Secondary Outcome Measures.

Performance measure	Day 90 mean ± SE; %	Six months mean ± SE; %	One year mean ± SE; %
Back Pain seven day average NRS	(n = 52)		
Improvement from baseline—absolute	2.5 ± 0.3 ( <i>p</i> < 0.0001)	Not recorded beyond	Not recorded beyond
Improvement from baseline—% change	36%	90 days per protocol	90 days per protocol
Responder Rate (% of subjects)	58% (30/52)		
Back Pain Single day NRS	(n = 52)	(n = 51)	(n = 47)
Improvement from baseline—absolute	2.5 ± 0.3 ( <i>p</i> < 0.0001)	2.2 ± 0.4 ( <i>p</i> < 0.0001)	2.4 ± 0.4 ( <i>p</i> < 0.0001)
Improvement from baseline—% change	35%	32%	33%
≥2 point improvement (% of subjects)	63% (33/52)	61% (31/51)	57% (27/47)
Disability ODI	(n = 52)	(n = 51)	(n = 47)
Improvement from baseline—absolute	13.4 ± 2.2 ( <i>p</i> < 0.0001)	11.6 ± 2.4 ( <i>p</i> < 0.0001)	14.3 ± 2.3 ( <i>p</i> < 0.0001)
≥10 point improvement (% of subjects)	52% (27/52)	57% (29/51)	60% (28/47)
QoL EQ-5D	(n = 52)	(n = 51)	(n = 47)
Improvement from baseline—absolute	0.213 ± 0.025 ( <i>p</i> < 0.0001)	0.184 ± 0.032 ( <i>p</i> < 0.0001)	0.219 ± 0.028 ( <i>p</i> < 0.0001)
≥0.03 point improvement (% of subjects)	88% (46/52)	82% (42/51)	81% (38/47)



**Figure 3.** Proportion of subjects with MCID in one, two, or all three key endpoints (NRS, ODI, and EQ5D).

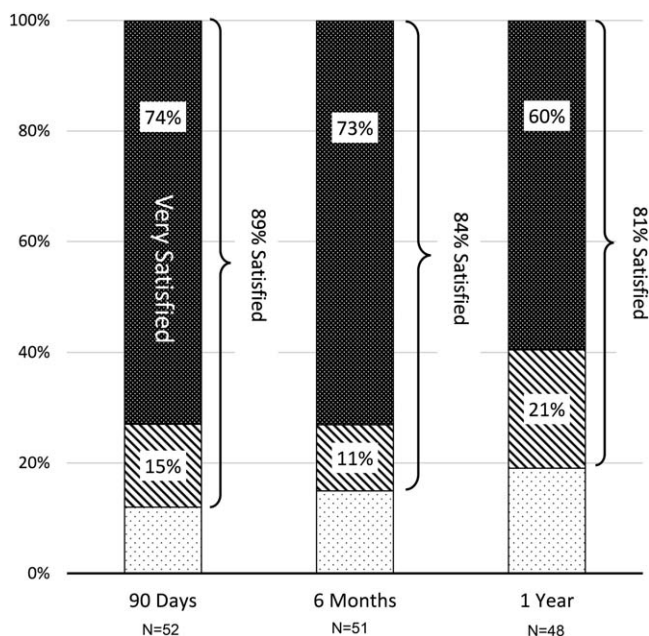
one year, 94%, 87%, and 87% of the subjects satisfied at least one or more MCID criteria and 40% or more had improvements in all three outcome measures.

**Exploratory Outcomes**

The TSQ showed that 89%, 84%, and 81% of the subjects were satisfied or very satisfied with their treatment at 90 days, six months, and one year, as illustrated in Figure 4.

**Device Use**

The IPG stores the start and stop time of each stimulation session which can be downloaded as a measure of compliance at each follow-up visit. Between activation and the 90-day visit, 86 ± 2% (52 ± 9.5 min/day—Mean ± SE) of the maximum 60 min total per day was used.



**Figure 4.** TSQ—Treatment satisfaction questionnaire.

**Table 4.** Summary of AEs to One Year Post Activation.

Relatedness	Total implanted subjects (n = 53)	
	SAE events N, % events (N, % subjects)	AE events N*, % events (N, % subjects)
Unrelated	3, 100% (3, 6%)	66, 46% (28, 53%)
Procedure, device, and/or stimulation	0 (0, 0%)	76, 54% (35, 66%)
Procedure related	0 (0, 0%)	14, 18% (11, 21%)
Device related	0 (0, 0%)	39, 51% (25, 47%)
Device/Procedure related	0 (0, 0%)	7, 9% (5, 9%)
Stimulation related	0 (0, 0%)	14, 18% (13, 25%)
Device/Stimulation related	0 (0, 0%)	2, 3% (2, 4%)

\*A subject can have more than one event in different categories; therefore, the total AEs does not equal the number of subjects.

After 90 days, the subjects determined their own daily use up to the maximum of 60 min per day, and for all subjects who had stimulation available for the entire time from implant to one year, 67% of available stimulation was delivered in the six months to one-year follow-up. Posthoc analysis did not reveal a correlation between amount of stimulation delivered and magnitude of outcome (pain, QoL, or disability). However, the high continuing use of stimulation indicates that subjects wanted to continue to deliver stimulation.

**Safety Outcomes**

At one-year post activation there were a total of 145 AEs with 69 (48%) unrelated; and 76 (52%) procedure, device, and/or therapy related events. The AEs are summarized in Table 4.

Of the 69 unrelated AEs, three were adjudicated as serious. One subject had a uterine fibroid surgically removed. Another subject was admitted to the hospital consequent to onset of chest pain, which was diagnosed via angiogram as noncardiac chest pain. The third subject had a cerebrovascular accident at nine months post implant.

None of the 76 related AEs were adjudicated as serious and none were unanticipated. Of the related AEs, 14 (18%) were procedure related (e.g., wound pain, inflammation, hematoma, postoperative discomfort), 39 (51%) were device related (e.g., loss of stimulation, pocket/lead discomfort), seven (9%) were device/procedure related (e.g., seroma/inflammation due to lead incision, postoperative nervous system irritation), 14 (18%) were stimulation related (e.g., undesired sensations, muscle fatigue), and two (3%) were device/stimulation related (e.g., undesired sensations). The most frequent AEs were loss of stimulation (23 AEs in 17 subjects), pocket discomfort (13 AEs in 12 subjects), and undesired sensations in the target area (seven AEs in six subjects). These three categories accounted for 57% of the related AEs. The remaining 33 related AEs occurred at rates of 1–5%.

**Device Deficiencies**

There were 70 reported device deficiencies of which 11% were at the time of implant (8 of 70), and all of these resolved prior to completion of implant surgery.

The majority of postimplantation device deficiencies were due to observation of high impedance (>5000 Ω) on one of the stimulation channels, most likely due to a break in a conductor in the lead. When high impedance is measured by the IPG on a channel being used for stimulation, the system will not initiate a stimulation

session. Stimulation can be resumed by reprogramming the IPG to use a different electrode configuration. In 94 leads implanted in 47 subjects using the lateral approach, high impedance was observed on at least one conductor in 44 leads in 28 subjects. Of the total of 28 subjects with high impedance observations, seven were reprogrammed to resume bilateral stimulation via a different electrode configuration, 13 had surgical revision to implant new leads, three subjects elected to continue therapy with unilateral stimulation, three had the system turned off, and two had the system explanted.

Investigation of the lead conductor fractures showed that the initially used lateral implant approach subjected the lead to a risk of tight bending as it traversed two planes of fascia that can move in different directions. The “midline approach” to reduce the risk of tight bending in the leads was introduced in all lead implants after the 47th subject, and experience to date indicates this approach has mitigated the risk of conductor fracture. Long-term follow-up of all subjects will yield additional data on the performance of the updated surgical approach.

From a total of 106 leads implanted using both the lateral (96 leads) and midline (12 leads) approach in 53 subjects, there was only one lead migration leading to a loss of stimulation.

## DISCUSSION

### Performance

The results should be viewed in light of the paucity of alternatives for this population with chronic intractable low back pain with average duration of more than 14 years and average NRS of 6.8 at the time of enrollment. None of the subjects were candidates for surgery or SCS, and none had obtained adequate pain relief with physical therapy and drugs.

The result shows that the composite outcome measure (MCID in one or more of NRS, ODI, and EQ5D) is close to the TSQ, implying that subject satisfaction is related to a combination of improvement in back pain, disability, and/or QoL vs. an improvement in any one specific outcome.

### Safety

None of the reported device, procedure, and/or stimulation related AEs, were serious or unanticipated.

The most common AE and device deficiency was loss of stimulation due to suspected conductor fracture. A modification to the implant approach has been introduced to mitigate this risk.

### Limitations

One limitation of this study was that it did not include a control arm. The ongoing ReActiv8-B Trial (clinicaltrials.gov identifier NCT02577354) includes a control arm with sham stimulation and results are anticipated in 2018.

The primary outcome measure in this study was improvement in pain evaluated with the NRS. However, evaluating changes in multiple outcome measures may be more clinically relevant—for example, many trials of spine surgery for low back pain use a composite outcome measure including assessment of disability.

Lead issues that result in loss of stimulation for a period of time may have negatively impacted the outcomes in the affected subjects.

Outcome data to one year are presented herein. Subjects in this study will continue to be evaluated annually through five years as part of a postmarket clinical follow-up study, which will provide information on longer term safety and efficacy.

The data from this trial have not been analyzed to explore patient parameters which could be predictive of outcomes, and further research is needed to more clearly identify the best candidates for this therapy.

## CONCLUSION

Despite the continuing prevalence of back pain worldwide, there are no satisfactory treatments available for people living with CLBP who are not candidates for surgery or SCS, and for whom conventional treatment (including physical therapy and drugs) do not provide adequate pain relief. One significant contributor to CLBP is functional instability at the intersegmental level due to lumbar multifidus dysfunction and the effects of arthrogenic muscle inhibition. In this trial, electrical stimulation to elicit episodic contraction of the lumbar multifidus resulted in clinically meaningful, statistically significant, and lasting improvements in back pain, disability, and QoL without any serious or unanticipated AEs related to the device, stimulation, or procedure. The outcomes from this trial demonstrate favorable efficacy and safety at one year in this difficult to treat patient population.

## Authorship Statement

Drs. Deckers, De Smedt, Mitchell, Vivian, Russo, Georgius, Green, Vieceli, Eldabe, Gulve, Van Buyten, Smet, Mehta, Ramaswamy, Baranidharan, Sullivan, and Gassin conducted the study, including patient recruitment, and data collection. Dr. Rathmell served as chair of the Clinical Events Committee and Dr. Gilligan served as chair of the Data Monitoring Committee. Drs. Deckers, Mitchell, Russo, Eldabe, van Buyten, and Baranidharan provided important intellectual input to the manuscript. We would like to thank Teresa Yurik from NAMSA for statistical support in analyzing the data and Steven Seme from Seme Device Consulting, LLC for scientific support. Peter Crosby of Mainstay Medical developed the first clinical trial protocol.

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## COMMENTS

This is an original multisite study evaluating the effectiveness of a novel neurostimulation technique of lumbar multifidus stimulation for chronic low back pain. Overall, the study is well described and the article is well-written. Although the majority of patients continued to do well at 12 month follow-up, the results of the study do indicate significant

problems with lead dysfunction in this early use of a new technique and device. Continued follow-up will hopefully provide us with more information on the utility of this procedure for patients with chronic low back pain of unknown etiology.

Kevin Vorenkamp  
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This study examined the outcome of a new neurostimulation device designed for restorative episodic contraction of the lumbar multifidus for treatment of chronic mechanical low back pain for the treatment of low back pain. The study is showed modest but clinically significant treatment outcomes. For low back pain, there have been proposed numerous treatments in the literature, which describe variable outcomes. Among these, there are facet joint blocks, sacroiliac joint blocks, various denervation techniques, various methods of treatment for discogenic pain, subcutaneous stimulation, spinal cord stimulation (in some instances), not to mention various medical, physiotherapeutic and psychotherapeutic or behavioral approaches. However, a significant socioeconomic low back pain problem for Western societies still remains. Thus, new concepts for low back pain treatment are urgently needed. I am curious to see, where exactly in the treatment algorithm of low back pain this new treatment option will find its place on the long run.

Tilman Wolter  
Freiburg

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As any of the 10 million angina suffers can opine, muscle pain is debilitating. Rarely treated by pain interventionalists, likely do to lack of understanding as well as limited and often inefficacious treatment options, skeletal muscle pain generates significant disability. There exists increasing evidence that inappropriate or imbalanced muscle firing patterns may contribute to significant morbidity, this commonly seen in syndromes such as patellar-femoral syndromes, and shoulder impingement syndromes. Chronic nonspecific low back pain may be a very similar animal. CNSLBP is ubiquitous, challenging to treat, a great medical-economic drain on the economy, and remains without definitive or even significantly effective treatment. This, as once of the first forays into direct neuromuscular electrical stimulation shows great promise. Particularly exciting, this approach is extra-spinal and thus conveys much reduced risk than traditional spinal cord stimulation, can be easily performed by nearly all implanters, and with already developed, improved techniques we will likely see a reduction in lead fracture and migration. Patient selection will of course improve outcomes as well. We await the forthcoming controlled study.. Well done!!

W. Porter McRoberts  
Fort Lauderdale, FL, USA

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This therapy addresses the subset of the patient population with chronic low back pain who are not good candidates for SCS and surgery. In my opinion, the one year data is promising. There is a concern about the high rate of device related AEs, but the authors have acknowledged it and are working to decrease the incidence of device related AEs.

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Comments not included in the Early View version of this paper.